STATEMENT

In 1953, Hynson, Westcott and Dunning, Incorporated ("Hynson") filed a new drug application ("NDA") for its drug Lutrexin (J.A. 3–4) with the Food and Drug Administration ("FDA"), pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)). Hynson recommended the drug, whose active ingredient, lututrin, is an extraction of pig ovaries, for use in the treatment of premature labor, threatened and habitual abortion, and dysmenorrhea (J.A. 3, 73, 166). The FDA, after examining the studies submitted with the application, informed Hynson that the studies were not sufficiently well controlled to justify the claims of effectiveness, and it particularly urged the manufacturer not to represent the drug as useful for threatened and habitual abortion (J.A. 3–4). However, because under the statute in effect at that time FDA was obliged to evaluate new drug applications solely upon consideration of the drug's safety, it permitted the NDA for Lutrexin to become effective in December 1953 (J.A. 3–4).[3] Two years later Hynson filed an NDA for Trexinest, another lututrin drug for which it made the same claims presented earlier for Lutrexin, and FDA, again on the basis of safety, permitted

[3] A review of the general background and history of the 1938 Act and the 1962 amendments thereto and FDA's administration of the legislation is set forth in our brief in *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72–555.

the NDA to become effective in 1956 (J.A. 4–5, 8–10).[4]

The 1962 Drug Amendments require FDA[5] to appraise drugs on the basis of their effectiveness for claimed uses as well as their safety. Accordingly, FDA contracted in 1966 with the National Academy of Sciences-National Research Council ("NAS–NRC") to assist it in the enormous task of reviewing efficacy claims for all drugs approved (as safe) between 1938 and 1962.[6] By order issued July 6, 1966, the Commissioner directed the holders of NDAs issued between 1938 and October 10, 1962, to submit the "most pertinent" data available concerning the effectiveness of their drugs (J.A. 193; 31 Fed. Reg. 9426). Hynson submitted a list of literature references, a copy of an unpublished study, and a representative sample testimonial letter on behalf of Lutrexin (J.A. 5–6).

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[4] In addition to 500 units of lututrin, each tablet of Trexinest contained 1.0 milligram of sodium estrone sulfate (J.A. 9). The effectiveness of sodium estrone sulfate is not questioned. Rather, the issue with Trexinest was whether the addition of lututrin brought any therapeutic benefits not conferred by the sodium estrone sulfate. Hynson has now discontinued the marketing of Trexinest.

[5] The Act speaks in terms of the Secretary of Health, Education, and Welfare. However, the Secretary has delegated this authority to the Commissioner of Food and Drugs. See 21 C.F.R. 2.120.

[6] A good description of the work and general conclusions of the NAS–NRC Study is found in *Drug Efficacy Study*, Final Report to the Commissioner of Food and Drugs, Food and Drug Administration, From the Division of Medical Sciences, National Research Council, National Academy of Sciences, Washington, D.C. (1969) (hereafter "NAS–NRC Report"). Ten copies of the study have been lodged with the Clerk of this Court.

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An NAS–NRC panel on drugs used in disturbances of the reproductive system reported to FDA that Hynson's claims of Lutrexin's effectiveness were either "inappropriate" or "unwarranted" in the absence of submission of further, proper documentation. The panel pointed out that the studies relied upon by the manufacturer were not well controlled, and it concluded that the drug was only "possibly effective" for its intended uses (J.A. 7–8).

On May 24, 1968, the Commissioner, after reviewing the report of the NAS–NRC panel, invited Hynson to submit further and sound documentation on the efficacy of Lutrexin (J.A. 10–11). Hynson submitted additional data (J.A. 28–29), but the Commissioner concluded that this additional information still failed to provide substantial evidence of the effectiveness of lututrin (J.A. 12). Accordingly, on March 22, 1969, he published notice of his intention to withdraw approval of Hynson's NDAs and offered Hynson the opportunity for a prewithdrawal hearing (J.A. 12–14). At that time, the agency's rules provided for a hearing upon timely request by any adversely affected party, and Hynson requested a hearing on April 18, 1969 (J.A. 14).

Before the hearing could take place, however, Hynson, on August 19, 1969, filed suit in the United States District Court for the District of Maryland seeking a declaratory judgment that its drugs were exempt from the efficacy review provisions of the 1962 Drug Amendments, or alternatively that there was no lack of substantial evidence of the drugs' efficacy (J.A.

15). The government responded with a motion to dismiss.

While the district court litigation was pending, FDA, on May 8, 1970, promulgated new regulations establishing minimal standards for "adequate and well-controlled investigations" as required under Sections 505(d) and 505(e) of the Act and limiting the right to a hearing to those applicants who supported their requests by a showing that such evidence exists (J.A. 487-491).[1] Shortly thereafter, the Commissioner wrote to Hynson asking the manufacturer to amend its request for hearing to provide supplementary data that would bring the request into compliance with the new regulations (J.A. 20-21). Hynson declined to amend its request, taking the position that its right to a hearing had already vested under the rules in effect at the time of its original request (J.A. 21-23).

FDA and Hynson agreed that, pending disposition of Hynson's suit by the district court, FDA would take no further steps in the withdrawal proceeding

[1] FDA had originally issued the regulations, in somewhat different form, on September 19, 1969. 34 Fed. Reg. 14596. However, on January 16, 1970, in an unrelated proceeding, the federal district court in Delaware enjoined the agency from carrying out the new regulations, holding that FDA had engaged in rule-making without conforming to the notice requirements of Section 4 of the Administrative Procedure Act. *Pharmaceutical Manufacturers Association* v. *Finch*, 307 F. Supp. 858 (D. Del.). FDA then solicited public comment and reissued the regulations, with certain changes, on May 8, 1970. The court subsequently upheld these regulations against a range of challenges, both substantive and procedural, in *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del.).

(J.A. 22–23). On September 16, 1970, Judge Northrup granted the government's motion to dismiss, ruling that FDA had primary jurisdiction and that Hynson had failed to exhaust its administrative remedies (J.A. 23–24).

After losing its lawsuit, Hynson, on October 16, 1970, renewed its request for an administrative hearing (J.A. 24), asking FDA to determine three questions: (1) whether there was a lack of substantial evidence of Lutrexin's effectiveness; (2) whether the drug was "grandfathered" under Section 107(c)(4) of the 1962 Drug Amendments; and (3) whether the drug was, because of alleged current general recognition of safety and effectiveness, not a new drug (J.A. 26). Although continuing to claim a vested right to a hearing under the former rules, Hynson submitted a list of material previously submitted to NAS-NRC or FDA, which it claimed constituted substantial evidence of Lutrexin's effectiveness under the new rules (J.A. 27–30). It also accompanied its request for a hearing on the jurisdictional questions with certain affidavits and reports of medical studies that had been submitted to the district court (J.A. 30–72, 87–121, 131–135).

On May 31, 1971, the Commissioner issued an order denying Hynson's request for a hearing and withdrawing approval of the NDA for Lutrexin (J.A. 72–78). The Commissioner held that Lutrexin was not exempt under Section 107(c)(4) because the NDA for Lutrexin had not been withdrawn prior to the enactment date of the 1962 amendments and was therefore

deemed approved thereunder (J.A. 74). The Commissioner further ruled that the new regulations governed Hynson's request for a hearing, and that Hynson had failed to satisfy the requirements of those regulations (J.A. 73–74). Turning to the substance of the submission, the Commissioner found that Hynson had not presented adequate and well-controlled clinical investigations in support of either its claim that Lutrexin is not presently a new drug or its claim that substantial evidence of effectiveness exists (J.A. 74, 77–78). He pointed out that, for the most part, Hynson had merely resubmitted a list of material previously submitted, that it had failed to point out what in the material was relevant, and that in any event the material "reveals a lack of adequate and well-controlled investigations showing that lututrin will have the effect HW&D claims for it" (J.A. 78). In a detailed review of Hynson's documentation, he demonstrated how each study showed deficiencies on its face that prevented it, under the rules, from being treated as an adequate and well-controlled study (J.A. 74–78).

On petition for review, the court of appeals reversed the Commissioner's withdrawal order (J.A. 181). While the court agreed with the Commissioner that Hynson's drugs were not exempt under Section 107 (c)(4) (J.A. 176–177),[8] it disagreed with his conclusion that Hynson was not entitled to a hearing on

[8] The court held that the exemption issue was one for the district court, not the agency, but, citing its opinion in *USV Pharmaceutical Corp.* v. *Richardson*, 461 F. 2d 223 (C.A. 4), it concluded that Hynson was not entitled to the exemption (J.A. 176). While ruling that only the district court could determine whether Hynson's product is currently a new drug,

the substantial evidence question. The court purported not to question the Commissioner's right to adopt regulations allowing denial of a hearing where no genuine substantial issue of fact is presented, and it presumed, without explicitly deciding, that this case is governed by the rules regarding availability of hearings that were in effect at the time of decision rather than those in effect at the time of Hynson's initial request for a hearing (J.A. 177).

Nonetheless, the court held that Hynson's submission had presented "'genuine and substantial' evidence that supports the position of the applicant" (J.A. 178). The court relied upon several factors: the "possibly effective" rating given the drug by the NAS-NRC panel; the absence of any record evidence of ineffectiveness; studies and opinions of medical experts of impressive credentials; and the affidavit of a former FDA medical officer that in his opinion Hynson had submitted adequate and well-controlled clinical investigations (J.A. 179–180). The Commissioner's efforts to demonstrate that deficiencies in Hynson's evidence made it inadequate under the statutory requirement for "adequate and well-controlled" studies were held to be unavailing. Such questions, the court stated, are to be resolved in an adversary hearing (J.A. 180).

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the court of appeals did not take issue on the merits with the Commissioner's holding that Lutrexin is a new drug (J.A. 176–177). The issue of FDA's right to decide this question is presented in *Hynson, Westcott and Dunning* v. *Weinberger*, No. 72–414, in *CIBA Corporation* v. *Weinberger*, No. 72–528, and in *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72–555.

SUMMARY OF ARGUMENT

In enacting the 1962 amendments to the Federal Food, Drug, and Cosmetic Act of 1938, Congress mandated for the first time that drugs sold to the American public must be shown to be effective for their recommended use as well as safe. It made this requirement applicable not only to new drugs coming on the market after 1962, but also to drugs that were covered by NDAs that had become effective between 1938 and 1962. Moreover, prompted by the testimony of numerous prominent experts in medicine and pharmacology, Congress adopted a rigorous standard for the kind of evidence that could be considered in support of a drug's efficacy claims, requiring "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved * * *." Uncontrolled studies and anecdotal reports and testimonials of practitioners based upon their experiences were rejected as unreliable evidence of efficacy.

FDA's implementing regulations spell out in detail the kinds of studies that are considered to be "adequate and well-controlled investigations" eligible to support drug efficacy claims. They further provide that a manufacturer seeking a hearing in connection with a proposed withdrawal of approval for an NDA must show that he is prepared to present evidence at the hearing consisting of "adequate and well-controlled investigations" as defined in the regulations; otherwise his request for a hearing will be denied.

Since claims not bottomed on evidence of this sort cannot be accepted under the clear statutory directive, the holding of a hearing in the absence of a threshold showing that such evidence may exist would be futile and is not required. *United States* v. *Storer Broadcasting Co.*, 351 U.S. 192; *Federal Power Commission* v. *Texaco, Inc.*, 377 U.S. 33.

The court of appeals committed two fundamental errors in ordering a hearing before the Lutrexin NDA could be withdrawn. First, it based its decision on a variety of factors—such as testimonials of physicians based upon their personal experience; the "possibly effective" rating given to the drug by the NAS-NRC review panel; and the absence of proof of ineffectiveness—none of which is, under the statute and regulations, the kind of evidence that could support a claim of effectiveness. If, notwithstanding the statutory "substantial evidence" requirement, FDA is to be obliged to hold hearings on the basis of such evidence (which is of a kind that any manufacturer can produce for virtually any product that has been on the market for a period of years), the agency will be mired in pointless hearings for years and will be frustrated in its efforts to carry out the congressional mandate to remove from the market drugs whose efficacy claims are not supported by scientifically sound evidence of effectiveness.

The second error of the court of appeals was the application of an improper standard of review to the Commissioner's determination that the studies submitted by Hynson with its request for a hearing failed on their face to qualify under the regulations as "adequate and well-controlled investigations." The Commissioner's order withdrawing approval of the Lutrexin NDA carefully evaluated each item submitted by the manufacturer and showed why it could not qualify. The court of appeals did not find that any of the Commissioner's conclusions were unreasonable, erroneous, or arbitrary, but simply ordered a hearing because something might come out at such a hearing that would show that the studies were not as defective as they appeared to be on their face. In so ruling, the court did not accord the proper deference to the Commissioner's expert determination that Hynson had failed to meet its burden of coming forward with a threshold showing that evidence existed warranting a hearing. By failing to respect the Commissioner's judgment in this highly technical area, even though it has not found the judgment to be unreasonable, the court has translated the statutory requirement to provide an opportunity for hearing into a mandate for the holding of numerous time-consuming, needless hearings that would greatly impede the agency's program to remove ineffective drugs from the market.

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ARGUMENT

I. THE FOOD AND DRUG ADMINISTRATION'S PROCEDURAL REGULATIONS PROPERLY IMPLEMENT SECTIONS 505(d) AND 505(e) OF THE ACT

A. THE STATUTE AND THE REGULATIONS ARE DESIGNED TO PROTECT THE PUBLIC BY IMPOSING EXACTING STANDARDS ON DRUG MANUFACTURERS TO SHOW THE EFFECTIVENESS OF THEIR PRODUCTS

The 1962 amendments to the Federal Food, Drug, and Cosmetic Act of 1938 are a landmark of American health legislation. They required for the first time that drugs sold to the American public be proven to be not only safe, but also effective, for their intended uses. As the House report on the legislation emphasized, the bill's purpose "better to protect the public health" was advanced by provisions requiring "that new drugs be shown to be effective as well as safe" and authorizing the "[w]ithdrawal of new drugs when their safety or effectiveness is no longer assured." H. Rep. No. 2464, 87th Cong., 2d Sess., pp. 1, 2.

Section 505(e) of the Act directs the Commissioner to refuse to approve a new drug application, or to withdraw approval of a new drug application previously approved, if the manufacturer fails to carry its burden of showing that there is "substantial evidence that the drug will have the effect it purports or is represented to have * * *." And further to "insure the reliability of drugs,"* Congress defined "substantial evidence" precisely and narrowly in Sec-

* S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess., p. 1.

tion 505(d) as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved * * *."[10]

The legislative history shows that the choice of this exacting standard was the result of a heightened congressional awareness that adequate and well-controlled clinical investigations are essential to determine drug effectiveness. As originally introduced by Senator Kefauver, the legislation would simply have added to existing Sections 505(d) and 505(e) of the Act the requirement that the drug be "efficacious in use," without providing a standard for measuring efficacy. S. 1552, 87th Cong., 1st Sess., Sec. 4(A)(9). However, hearings on the bill produced testimony from eminent physicians that anecdotal, uncontrolled evidence was not reliable, and that controlled clinical testing was necessary to make an adequate determination of drug effectiveness. As Dr. May, Professor of Pediatrics at New York University, succinctly stated: "A collection of impressions will not furnish the truth—this approach did not prevent doctors from having unbounded faith in the curative powers of leeches for hundreds of years before scientific evaluation became the preferred means of judging efficacy of therapy."[11]

[10] The same standard of "substantial evidence" is made applicable to antibiotic drugs by Section 507(h) of the Act (21 U.S.C. 357(h)).

[11] Hearings before the Subcommittee on Antitrust and Monopoly, Senate Committee on the Judiciary, on Drug Industry An-

Accordingly, when the Judiciary Committee reported the bill to the Senate in July 1962, it included provisions authorizing the Secretary to refuse to permit an NDA to become effective or to suspend the effectiveness of an NDA if "there is a lack of substantial evidence (including substantial clinical evidence), supported by investigations of experts qualified by scientific training and experience to evaluate the effectiveness of drugs, that the drug will have the effect it purports or is represented to have * * *." S. Rep. No. 1744, Part 1, 87th Cong., 2d Sess., pp. 25–26. And the Committee explained that "therapeutic claims for new drugs [must] be supported by reliable pharmacological and clinical studies." *Id.* at 16.

Before the Senate could act, however, the Judiciary Committee met again and reported new, stronger amendments.[12] Speaking of the language which became Section 505(d)'s definition of "substantial evidence," the Committee stated that it "clarifies and strengthens the previously reported bill by restating

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titrust Act, 87th Cong., 1st Sess., Part 1, p. 195 ("Hearings").

Other distinguished witnesses confirmed these remarks. See, *e.g.*, Hearings at 282, where Dr. Lasagna emphasized the importance of double-blind studies, and at 411–412, where Dr. Dowling spoke of the importance of placebo effect and of elimination of bias in selection and testing of patients. See *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301, 307–308 (D. Del.), for a further review of the legislative history underlying adoption of the definition of "substantial evidence."

[12] The impetus for the new consideration came from public concern over the thalidomide incident and pressure from the President for stronger legislation. S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess., p. 1.

and carefully defining the quality and quantum of evidence which the Secretary must find to exist as a basis for clearance of the drug or for withdrawal of a previously approved new-drug application." S. Rep. No. 1744, Part 2, *supra*, at p. 6. The Committee explained that "* * * a claim could be rejected if it were found (a) that the investigations were not 'adequate'; (b) that they were not 'well controlled'; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which the application is made; or (d) that the conclusions drawn by such experts could not fairly and responsibly be derived from their investigations." *Ibid.* Thus the history of the "substantial evidence" provisions of the Act shows increasingly stringent statutory language culminating in the provision that is now the law.

Since Congress insisted that "substantial evidence" consist only of "adequate and well-controlled investigations," FDA promulgated regulations defining the form such investigations should take. The need for these regulations became particularly clear in light of the experience of the NAS–NRC Drug Efficacy Study Group, which at the conclusion of its efforts in 1969 informed the Commissioner that "[t]he lack of substantial evidence based on well-controlled investigations by experienced investigators was conspicuous." NAS–NRC Report, p. 13.

The agency's carefully drawn regulations express well-established principles of scientific investigation, many of which were specifically referred to by doctors in congressional hearings on the 1962 Drug Amend-

ments. 35 Fed. Reg. 7250. Thus, the regulations require a clear statement of the objectives of the study and a method of subject selection and assignment to test groups that assures their suitability for the purposes of the study, minimizes bias, and assures comparability of pertinent variables such as patient age and disease severity. The researcher must explain the methods of observing and recording results. There must be an unbiased comparison with control groups under one or more of the following types of control: no treatment, placebo, active treatment, and historical. There must also be a statistically valid summary of methods and evaluation of results. While uncontrolled or partially controlled studies are unacceptable as the sole basis for approval of claims of effectiveness, they may, if carefully conducted and documented, be used to corroborate well-controlled studies. On the other hand, random experience, isolated case reports, and reports lacking the details which permit scientific evaluation will not be considered. The regulations also provide for waiver of any of the criteria upon a request and showing by a manufacturer that they are not reasonably applicable (J.A. 489).

Just as the NAS–NRC Study had alerted the Commissioner to the existence of large numbers of drugs for which there was a lack of substantial evidence of effectiveness, it had at the same time pointed up the need to develop procedures by which the agency could expeditiously carry out its duty of removing such drugs from the market. The study had covered approximately 4,000 drug products for which NDAs had

been obtained between 1938 and 1962. NAS–NRC Report, p. 5. Many of these products have been offered to the public for use in the treatment of more than one condition, so that, altogether, the NAS–NRC panels evaluated approximately 16,500 claims made on behalf of these 4,000 products. About 70 percent of these claims were found not to be supported by substantial evidence of effectiveness.[11] Indeed, only 434 drug products were found effective for all their claimed uses, leaving more than 3,500 as to which withdrawal of approval with respect to at least one claim is in prospect. If FDA were obliged to grant hearings on demand before withdrawing approval for each of these products, the agency would be mired in hearings for years, and it is difficult to see how or when the agency would be able to complete its fundamental task under the 1962 amendments of removing drugs of unproved effectiveness from the market.

FDA accommodated its responsibility to remove ineffective drugs from the market with its obligation under Section 505(e) to grant manufacturers an "opportunity for hearing" by adopting regulations re-

[11] See Hearings before the Subcommittee on Monopoly of the Senate Select Committee on Small Business on Competitive Problems in the Drug Industry, 92d Cong., 1st Sess., Part 20, pp. 7975–7976. The distribution of these claims among the various rating categories used by NAS–NRC was as follows: Ineffective—14.7%; possibly effective—35%; probably effective—7.3%; effective "but"—24%; effective—19.1%. The figure quoted in the text results from a redistribution of the "effective 'but'" group into the other categories. The meaning of the various categories utilized for rating purposes by the NAS–NRC panels is explained in the NAS–NRC Report, pp. 42–43. See also pp. 28–29, *infra*.

quiring the manufacturer to submit studies apparently constituting adequate and well-controlled investigations as defined in the regulations in order to obtain a hearing on the proposed withdrawal of an NDA (J.A. 490–491).[14] The manufacturer must submit an analysis of the data which he is prepared to prove at the hearing, and he must set forth specific facts "showing that there is a genuine and substantial issue of fact that requires a hearing" (J.A. 491).[15] If it clearly appears that there is no such issue of fact—for example, that adequate and well-controlled clinical investigations have not been identified in support of the claims of effectiveness—the Commissioner will then enter an order, with appropriate findings and conclusions, withdrawing approval of the NDA (J.A. 491). That is what occurred in the instant case, and, we submit, respondent was thereby afforded the "opportunity for hearing" required by Section 505(e) of the Federal Food, Drug, and Cosmetic Act, *supra*. It is a disposition similar in some respects to a trial court's granting of a motion for summary judgment when there

[14] Substantially the same regulations apply to proceedings for removal of ineffective antibiotics from the market. See 21 C.F.R. 146.1(d).

[15] The nature of the problem is such that formal hearings are not likely to be needed in many instances. If studies exist that appear on their face to constitute adequate and well-controlled investigations as defined in the regulations, the Commissioner would, in the absence of unusual circumstances, find the drug effective and not pursue withdrawal of its NDA. If the manufacturer is unable to make a *prima facie* showing that such studies exist, a hearing would be useless.

are no legally relevant controverted facts to be decided or to the granting of a motion to dismiss a complaint for failure to state a claim on which relief can be granted. In this sense, the applicant has had full opportunity to make his basic case and has been heard, and, as we explain *infra* (pp. 33–35), the agency's denial under its regulations of a fuller hearing on the facts of this case is subject to appropriate judicial review.

B. THE REGULATIONS ARE VALID

The regulations defining what constitutes "adequate and well-controlled investigations" conforming to the statutory requirement have been upheld whenever challenged in the past. *Upjohn Co.* v. *Finch*, 422 F. 2d 944 (C.A. 6); *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del.). Their validity is not at issue in this case.

Nor has either side petitioned this Court to review the conclusion of the court of appeals that the regulations conditioning the availability of a hearing on the establishment of a genuine and substantial issue of fact (by specifying the existence of adequate and well-controlled clinical investigations) are valid on their face. The only mention of this issue came in Hynson's Brief in Opposition, filed after the 90-day period for petitioning for certiorari had expired, wherein Hynson stated that, if the government's petition were granted, it "would want to place * * * before this court" the question of the validity of the regulation (Br. in Opp., p. 3). There is thus some

doubt whether the issue is properly before this Court. Since, however, it could be argued that invalidation of the regulation on availability of hearings would constitute an alternative ground for affirmance of the judgment below, we discuss this question here and contend that the regulation is valid.

The procedural regulation governing the right to a hearing dovetails with the substantive regulations defining what can be considered "adequate and well-controlled investigations," the statutory precondition to a finding that "substantial evidence" of effectiveness exists. It reflects a "threshold requirement" for a hearing. *American Cyanamid Co.* v. *Richardson*, 456 F. 2d 509, 513 (C.A. 1).[16] The regulation does no more than place upon the party demanding a hearing the responsibility to present "the evidence needed to make out a *prima facie* case." *Ciba-Geigy Corp.* v. *Richardson*, 446 F. 2d 466, 468 (C.A. 2). A hearing would be a time-consuming and useless formality unless the manufacturer is prepared to present evidence of the precise type that is required by statute and valid regulation thereunder to support a claim of effectiveness.

Thus, the regulations work in a manner closely akin to those upheld by this Court in *United States* v. *Storer Broadcasting Co.*, 351 U.S. 192, where the Federal Communications Commission, relying on its newly promulgated regulation limiting one person to ownership of five television stations, dismissed without hearing Storer's application for a sixth station. This

[16] The *American Cyanamid* decision was by Judge Coffin alone, denying a motion for stay of an order of withdrawal.

Court affirmed the Commission's regulation and its action thereunder as consistent with the hearing provision of Section 309(b) of the Communications Act, observing that Congress had not "intended the Commission to waste time on applications that do not state a valid basis for a hearing." *Id.* at 205. Similarly, in *Federal Power Commission* v. *Texaco, Inc.*, 377 U.S. 33, 39, the Court dealt with a situation precisely parallel to that here:

> * * * [T]he statutory requirement for a hearing under § 7 does not preclude the Commission from particularizing statutory standards through the rulemaking process and barring at the threshold those who neither measure up to them nor show reasons why in the public interest the rule should be waived.

The courts of appeals have similarly declined to insist upon the holding of hearings when there are no material issues of fact to be resolved. See, *e.g.*, *Municipal Light Boards* v. *Federal Power Commission*, 450 F. 2d 1341, 1345 (C.A.D.C.); *Citizens for Allegan County* v. *Federal Power Commission*, 414 F. 2d 1125, 1128 and n. 5 (C.A.D.C.); *Virginia Electric and Power Co.* v. *Federal Power Commission*, 351 F. 2d 408, 410 (C.A. 4). Moreover, the Administrative Conference of the United States has recommended that all agencies adopt rules for summary decision, 38 U.S.L.W. 2658, and several other agencies currently have similar rules dispensing with a hearing when there is no genuine issue of fact to be determined. See, *e.g.*, 16 C.F.R. 3.24 (Federal Trade Commission); 29 C.F.R. 102.24 (National Labor Relations Board).

Applying these principles to the present situation, if a manufacturer is not prepared to present data derived from the kind of adequate and well-controlled investigations required by the statute and FDA regulations, a hearing would be as much a waste of time as in *Storer* or *Texaco*. It is not surprising, then, that every court that has ruled on the question, including the court of appeals in the instant case, has upheld the lawfulness of the Commissioner's regulations (J.A. 177; *Ciba-Geigy Corp.* v. *Richardson*, 446 F. 2d 466 (C.A. 2); *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del.); *Upjohn Co.* v. *Finch*, 422 F. 2d 944 (C.A. 6); *Pfizer, Inc.* v. *Richardson*, 434 F. 2d 536 (C.A. 2)). It is thus clear that the regulations conform to the statute and to administrative due process.[17]

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[17] Hynson has also indicated in its Brief in Opposition (p. 8) that it will seek to argue the question whether it was entitled to a hearing because its original hearing demand preceded adoption of the "summary judgment" regulations. This question too was not presented in either certiorari petition in this case. It is, in any event, an unmeritorious contention. Since Hynson has never had adequate and well-controlled clinical investigations substantiating the efficacy of Lutrexin, there has never been anything to be determined in an adjudicatory hearing. The change in FDA's procedural regulations merely made explicit what had previously been implicit—that FDA need not hold a hearing if there are no material issues of fact to be determined.

In any event, *Storer* is dispositive of this contention, since the Court there held lawful the five-station regulations and their applicability to *Storer* although the Commission had issued them after Storer had filed its application for a sixth station (351 U.S. at 205). Similarly, here the Commissioner had the right to make the May 1970 regulations applicable to all

II. THE COURT OF APPEALS ERRED IN HOLDING THAT THE COMMISSIONER IMPROPERLY DENIED HYNSON A HEARING

The Commissioner denied Hynson's request for a hearing because it clearly appeared from examination of the data submitted that none of the studies upon which Hynson relied were adequate and well-controlled clinical investigations as required by the regulations (J.A. 74, 78). The court of appeals reversed, holding that the Commissioner's objections "* * * do not justify a final conclusion, made *ex parte*, without a hearing, that it 'clearly appears' that there is no genuine issue of fact on the effectiveness of Lutrexin * * *" (J.A. 180). We believe that the court of appeals seriously misconstrued the meaning of the regulations whose validity it upheld and did not give proper weight to the determination of the Commissioner.

A. THE COURT OF APPEALS FAILED TO APPRECIATE THE HIGHLY PARTICULARIZED SHOWING OF SUBSTANTIAL EVIDENCE OF EFFECTIVENESS REQUIRED BY THE STATUTE AND THE REGULATIONS

Section 505(e) of the Act requires the withdrawal of the NDA of any drug when "there is a lack of substantial evidence" of the drug's effectiveness. Sec-

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persons as to whom NDA withdrawal proceedings were then pending. In *Upjohn*, *supra*, the court of appeals upheld agency action denying Upjohn a hearing on September 19, 1969, on the basis of regulations promulgated that very day. And see, generally, *Thorpe* v. *Housing Authority*, 393 U.S. 268, 281–283.

tion 505(d) defines "substantial evidence" to mean "adequate and well-controlled investigations, including clinical investigations, by experts" which enable experts to conclude that the drug will have the effect claimed for it. And FDA's regulations spell out with particularity what kinds of clinical investigations are adequate and well-controlled. Thus the holder of an NDA must show the effectiveness of his drug by the kind of clinical investigations that the statute and the regulations demand, and this substantive requirement shapes the procedural issue of what a manufacturer must show in order to gain a hearing. He must, by the data he submits, make at least a "threshold"[18] or "*prima facie*"[19] showing that his evidence is of the precise type the statute and regulations require. If he fails in that showing, he has failed to establish that there is any legally relevant issue of fact meriting a hearing, and in such circumstances a hearing would be a waste of time. *Storer Broadcasting, supra,* 351 U.S. at 205.

The court of appeals, however, did not appreciate this linkage between the substantive standards for effectiveness and the procedural requirements for a hearing. The court stated that the issue before the Commissioner was "the effectiveness of Lutrexin" (J.A. 180). This is too broad and imprecise a formulation of the relevant issue. The issue on the request for a hearing is not generally the "effectiveness" of the drug, but, much more narrowly, whether there is a

[18] *American Cyanamid, supra,* 456 F.2d at 513.

[19] *Ciba-Geigy Corp., supra,* 446 F.2d at 468.

showing of substantial evidence of effectiveness defined the way the statute and the regulations define it. Since Congress has directed that only adequate and well-controlled clinical investigations will qualify as substantial evidence of a drug's effectiveness, and the Commissioner's regulations properly give content to the congressional standard, evidence of that kind must be presented to get a hearing.

As a result of this misunderstanding, the court held relevant to the issue of a hearing various criteria which have no relevance to the critical question whether the manufacturer can produce substantial evidence of the necessary kind:

1. Thus, the court noted that no qualified expert had stated that Lutrexin was ineffective for its intended uses (J.A. 179). But this is doubly irrelevant: the statute and the regulations do not require FDA to prove a drug ineffective, but rather oblige the manufacturer to show substantial evidence of effectiveness. See *Ubiotica Corp.* v. *Food and Drug Administration,* 427 F.2d 376, 378 (C.A. 6). Moreover, the manufacturer must show effectiveness by very specifically defined "substantial evidence," and absence of expert condemnation of a drug as ineffective in no way meets the substantial evidence requirements of the Act and the regulations.

Indeed, Congress has in one respect been lenient in establishing the burden of proof of efficacy that the manufacturer must shoulder. He need not prove that the drug is effective beyond a reasonable doubt or even by a preponderance of the evidence. As stated in

the NAS–NRC Report (p. 8), "claims for effectiveness should be accepted if a substantial amount of well-documented favorable evidence is presented, even though there may also exist a weighty body of inconclusive or negative evidence." See also S. Rep. No. 1744, Part 2, *supra*, at p. 6. FDA has never sought to impose a weightier burden. But where the manufacturer is, as here, unable to point to *any* evidence of the necessary quality, there is no point in launching an inquiry whether a "substantial" quantum of such evidence exists.

2. Similarly, the court of appeals' reference to the "possibly effective" rating given Lutrexin by the NAS–NRC review panel misses the mark—all the more so in view of the fact that the panel pointedly noted the manufacturer's failure to produce well-controlled studies (J.A. 7). A "possibly effective" rating, far from constituting substantial evidence of effectiveness as defined by the statute and regulations, instead reflects a lack of such evidence in support of the drug. Cf. *American Public Health Assn.* v. *Veneman*, 349 F. Supp. 1311, 1314 (D.D.C.). The instructions to the panels directed use of the "possibly effective" rating in the following circumstances (NAS-NRC Report, p. 42):

> In relation to the indication in question, there is little evidence of effectiveness under any of the criteria stated above. The possibility that additional supporting evidence might be developed should not be ruled out, however. The recommendations to the FDA could be that unless it is informed that studies are being initiated

> promptly with the object of developing substantial evidence of effectiveness, the indication in question should be considered inappropriate.

The report observed that "[t]he definition [of substantial evidence] in the law is an exacting one. Had the panels adhered rigidly to it, a great many claims would have been rejected on the grounds that they were not supported by substantial evidence * * *" (*id.* at 8). It indicated that, in such circumstances, the intermediate ratings of "probably effective" and "possibly effective" were assigned "on the basis of [the panel members'] own clinical experience with the drug and their evaluation of the opinions of their peers" (*id.* at 9).

Nearly 6,000 of the 16,500 claims evaluated by NAS–NRC received "possibly effective" ratings (see n. 13, *supra,* and accompanying text), and if such a rating entitles the manufacturer to an evidentiary hearing, FDA would be obliged to hold hearings on thousands of claims with respect to which the manufacturer had not produced any evidence meeting the requirements of law.

3. The court evidently was also impressed that several physicians of high professional standing believe Lutrexin to be effective (J.A. 179). However, unless such views are premised on properly conducted investigations, they are not of significant probative value under the law. Manufacturers can almost always produce, as Hynson did (J.A. 29, 32–58), affidavits or testimonial letters from qualified physicians proclaiming their belief in the efficacy of the manufacturer's

product. But this is precisely the type of anecdotal evidence that Congress rejected as unreliable for the purposes of the 1962 amendments (see pp. 15–16, *supra*) and which the regulations rightly hold will not be considered in determining whether there is a lack of substantial evidence of efficacy (J.A. 490). If the agency were compelled to conduct a full evidentiary hearing in every case in which this type of proof is offered, decades might pass before it would be able to complete its fundamental task under the 1962 amendments of removing from the market drugs of unproved effectiveness.[20]

Thus, despite the court's professed intention to uphold the validity of the regulations, its reliance on evidence which is not "substantial" to direct a hearing effectively nullifies those regulations and renders implementation of the statute virtually impossible.

[20] Recognition of FDA's ability to withdraw approval of NDAs without an evidentiary hearing when the manufacturer is unable to make the threshold showing of the existence of studies that could constitute substantial evidence of effectiveness is particularly important in view of the fact that FDA is currently under court order to proceed with greater dispatch in evaluating the efficacy of drugs studied by NAS–NRC and removing from the market those not shown to be effective. *American Public Health Association* v. *Veneman*, 349 F. Supp. 1311 (D.D.C.). The court's order obliges the Commissioner, by October 10, 1976, to give notice of opportunity for hearing and to rule on all requests for hearing in connection with all such drugs not found by him to be effective. The agency is currently laboring to carry out the court's order punctually, but its efforts will be of little avail and of no benefit to the public if all that is accomplished is to bring nearer the holding of hundreds or thousands of pointless hearings.

B. THE COURT OF APPEALS ALSO ERRED IN REVERSING THE COMMISSIONER'S DETERMINATION THAT THE STUDIES WHICH HYNSON PRODUCED TO SUPPORT ITS CLAIM FOR A HEARING WERE NOT ADEQUATE AND WELL-CONTROLLED CLINICAL INVESTIGATIONS AS DEFINED BY THE REGULATIONS.

1. The Court of Appeals Applied an Erroneous Standard of Review.

The court of appeals, as we have pointed out in the preceding section, erroneously considered irrelevant factors in deciding that Hynson was entitled to a hearing. The court also applied an erroneous standard of law to the Commissioner's appraisal of those studies which Hynson did send him that were claimed to be in conformity with the procedural regulations.

After losing its district court suit against the Commissioner (J.A. 23–24), Hynson submitted data to FDA which it claimed to be substantial evidence within the meaning of the regulations and to be sufficient to warrant a hearing (J.A. 27–32). By then, Hynson had had eight years from the enactment of the 1962 amendments within which to develop the kind of substantial evidence of effectiveness required by the Act (the two-year statutory grace period provided by Section 107(c)(3) of the 1962 legislation and six additional years). Although the regulations required an applicant to provide "a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove" (J.A. 491), Hynson sent the Commissioner a heterogeneous and unorganized mass

of documents ranging from testimonial letters to court pleadings (see J.A. 27–32).

From this material, the Commissioner culled the medical studies. Several of the studies were papers which Hynson had already sent to him in the past,[21] but he nonetheless examined them all in terms of the applicable substantial evidence regulations. He then gave a careful and well-reasoned explanation [22] of why Hynson had failed to present a threshold showing that its studies were adequate and well-controlled clinical investigations within the meaning of the substantial evidence regulations (J.A. 74–78). Hynson now admits that many of those studies "do not pur-

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[21] For example, Hynson had first sent the Commissioner the papers by Gratton (J.A. 87–92), Gray (J.A. 131–135), and Majewski (J.A. 106–111) in 1968 (J.A. 28).

[22] Because the Commissioner's order was thorough and reasoned, it does not suffer from the lack of findings which the court of appeals held grounds for reversal in *USV Pharmaceutical Corp.* v. *Secretary of Health, Education, and Welfare*, 466 F. 2d 455, 461–462 (C.A.D.C.), a decision in proceedings related to those involved in No. 72–666. The *USV* decision, *supra*, also holds that the Commissioner may not simply rely on the reports of the NAS–NRC panels to call upon the holder of an NDA issued prior to October 10, 1962, to produce evidence of effectiveness establishing his right to a hearing or lose approval of the NDA. *Id.* at 461. We disagree. Congress wanted to make sure that drugs were effective: both those that had come on the market before 1962 and those that came on after 1962. In furtherance of that statutory purpose, the Commissioner may, by adopting the findings of the NAS–NRC panels, rightly place upon the holder of NDAs issued prior to October 10, 1962 (when it was not necessary to submit any proof of effectiveness to receive approval of an NDA) the burden of coming forward with substantial evidence of effectiveness, to avoid withdrawal of the approval of that NDA.

port to be controlled studies" (Br. in Opp., No. 72–394, p. 13) and thus do not measure up to the regulations. The critical shortcoming of the others are, we submit, clearly and correctly exposed in the Commissioner's decision. See pp. 36–38, *infra*.

The court of appeals assumed for purposes of its decision the correctness of the Commissioner's critique of Hynson's studies, but it held that "at most" the critique only created an issue of fact on the adequacy of the studies to be resolved at a hearing (J.A. 180). Although the court's reasoning is not free from ambiguity, it appears to rest on the premise that a hearing is necessary so long as there remains a possibility that some evidence of the necessary kind will turn up at the hearing, even if the Commissioner has reasonably determined that the manufacturer has at the threshold stage failed to produce any.[23] This reasoning misconceives the respective roles of agency and reviewing court and seriously undermines the regulations.

The Commissioner's determination that a manufacturer has failed to make even a threshold showing of the existence of studies that could qualify as "substantial evidence" is, to be sure, subject to judicial review. Such a determination, however, involving the appraisal of technical medical studies in light of the

[23] It is possible that the court of appeals meant to hold that a hearing is necessary before the Commissioner may determine whether a manufacturer has made a threshold showing of "substantial evidence" as required by the regulations. But this would require a hearing in every case and would thus be inconsistent with the court's professed belief in the validity of the procedural regulations (J.A. 177).

standards of the regulations, necessarily requires to a high degree the use of expertise particularly within the province of FDA and notably not the strength of courts. See, *e.g.*, *United States* v. *Bacto-Unidisk*, 394 U.S. 784, 791–792. As Judge Friendly observed in a decision upholding a similar determination of the Commissioner to deny a requested hearing: "* * * such a determination is peculiarly within the FDA's expertise and we would be reluctant to intrude into medical matters we do not truly understand * * *." *Pfizer, supra,* 434 F. 2d at 546.[24] This, of course, does not mean that the courts are to abdicate their reviewing function, but it does mean they should perform that function with awareness of the respective competencies of court and agency. A reviewing court should determine whether the Commissioner has articulated the grounds of his decision, whether they are consistent with the statute, and whether they are supported by the evidence. In short, if the Commissioner's decision shows "that the FDA had a reasonable basis for considering that * * * [the manufacturer's] submissions did not comply with the requirement of the statute, and the Regulation" (*id.* at 547), the court should affirm.

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[24] In *Pfizer*, as in the present case, the manufacturer submitted studies which it claimed were adequate and well-controlled clinical investigations showing the efficacy of its drug (an antibiotic) and entitling it to a hearing. The Commissioner reviewed the studies, pointed out their deficiencies, and denied a hearing. 434 F. 2d at 546–547. In *Upjohn*, *supra*, the same contention was made by the manufacturer, who had submitted 54 documents in support thereof, and was rejected by the Commissioner and the court (422 F. 2d at 951).

The decision of the court below, by contrast, requires of the Commissioner more than articulate reasonableness: it requires the exclusion of any possibility that a hearing might result in production of substantial evidence of effectiveness. And, expert as the Commissioner is, this is a burden that he should not be expected to carry. It is possible that, in some rare instances, a hearing would produce new information justifying a different conclusion about a given question. In some situations, but not here, one could not automatically rule out the possibility that examination of the authors and the reliability of their investigations, as suggested by the court of appeals (J.A. 180), might ultimately show that their studies met the requirements of the regulations. But there is no obligation on the Commissioner, after he has made a reasonable determination that the studies fail to conform to the regulations, to negative the almost endless, if remote, possibilities that a hearing might still turn up relevant evidence. Surely neither the statute nor the regulations require the Commissioner to hold a hearing on the basis of such speculative possibilities. For to require a hearing in such circumstances would in effect be to require a hearing in every case, and the Commissioner's procedural regulations, though never formally struck down, would be as ineffective as if invalidated.

2. *The Commissioner Properly Determined That the Studies Submitted by Hynson Do Not Meet the Requirements of the Regulations.*

Under a proper standard of review, the court of appeals should have ruled that the Commissioner correctly denied Hynson's request for a hearing. Hynson submitted (or referred the Commissioner to) a pair of studies written in the 1950's by Rezek (J.A. 112–121), four papers by Trythall (J.A. 135–148),[25] and articles by Gray (J.A. 131–135), G. Jones and Smith (J.A. 160–167), and S. Jones (J.A. 167–171). Since Hynson now concedes that these "do not purport to be controlled studies" (Br. in Opp., No. 72–394, p. 13), there is no need to rehearse the Commissioner's findings that these studies failed to conform to the regulations (J.A. 76–78).

Hynson also submitted to the Commissioner two papers written in the mid-1950's reporting on a study by Majewski and Jennings (J.A. 92–105), who concluded that "Lutrexin is successful in controlling uterine contractions * * *" (J.A. 105). As the Commissioner explained, severe deficiencies in the study prevent it from meeting the standards of the regulations. For example, the authors admitted that some patients had received medication in addition to Lutrexin (J.A. 97, 101). As the Commissioner properly observed, "[t]here is no way to determine the percentage of patients on concurrent medication or whether the results of the study were thereby influenced" (J.A. 75). By not stating what other drugs they used, in what amounts, and to whom they were administered, Majewski and Jennings plainly failed to meet the requirement of the regulations that the study's plan and re-

[25] Two of the Trythall papers are not printed in the Joint Appendix.

port "* * * must include * * * (2) A method of selection of the subjects that * * * (iii) Assures comparability in test and control groups of pertinent variables, such as * * * use of drugs other than the test drug" (J.A. 487–488). Similarly, the authors, although freely using statistics, did not give a summary or explanation of their statistical methodology and thus failed to conform to the requirement of the regulations that there must be a summary of methods, "including any appropriate statistical methods" (J.A. 489).[25]

Hynson also submitted an unpublished article written in 1968 by Gratton, who reported good results with Lutrexin in the treatment of prematurity (J.A. 87–92) in patients who were claimed to have served as their own controls (J.A. 89). Even if this method of control were acceptable, the study does not meet the requirements of the regulations (J.A. 487–488) because the use of numerous medications concurrently makes impossible a scientific attribution of the results to Lutrexin; the method of selecting patients, who were not shown to be representative of the population about which inferences were made, is not explained; and the pairing of different patient groups lacked adequate statistical design and evaluation.

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[25] Without reasoned explanation of the statistical methods, it is not possible to tell whether the results in the test group were due to chance or to some kind of bias (J.A. 75). Statistical infirmities, ranging from inadequate definition of the subject population to inaccurate comparisons of patients within the test group (J.A. 75–76), also mark Majewski's unpublished 1968 paper (J.A. 106–111).

The deficiencies of Hynson's studies, as elucidated by the Commissioner, thus justify his determination that none of the studies are adequate and well-controlled clinical investigations within the meaning of the regulations." We need not speculate on what the results of the proceedings might have been had Hynson requested a waiver of the criteria of the regulations, as it had a right to do (J.A. 489), since Hynson never requested a waiver.

Nor, contrary to the opinion below (J.A. 180), is the Commissioner's decision vitiated by the affidavit of Dr. Sadusk, which Hynson submitted (J.A. 58-59). Although the court states that the Commissioner "disregards the categorical opinion of his former Director of the Bureau of Medicine and Medical Director [Dr. Sadusk][28] that the clinical tests and investigations submitted by the appellant [sic] represented '"well-controlled" clinical studies'" (J.A. 180), this is erroneous in two respects. First, the Commissioner did not disregard the views of Dr. Sadusk. See J.A. 77. Second, Dr. Sadusk never stated that the studies which Hynson submitted were well-controlled. Indeed, Dr. Sadusk's affidavit does not even mention Hynson's

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[27] Contrary to Hynson's suggestion (Br. in Opp., No. 72-394, pp. 10-12), the fact that one of the studies sought to use historical controls was not the reason for the Commissioner's rejection of it. The regulations make provisions for the use of historical controls (J.A. 488-489). Rather, the Commissioner's criticism was that the author's use of historical control was inadequate (J.A. 77).

[28] Dr. Sadusk left the employ of the Food and Drug Administration in 1967 and at the time of his affidavit (January 22, 1970) was a vice-president of Parke, Davis & Company, a large pharmaceutical manufacturer (J.A. 59-63).

studies—all of which were written well before his affidavit—and, for all the affidavit states, he never even saw them.

What the affidavit does say is that double-blind studies or placebo controls may be unethical, immoral or illegal in certain cases, that cases involving threatened and habitual abortion and premature labor may be such cases, and that in such cases studies "based on statistics, or historical controls (including patient's own history) may well be expected to produce 'well controlled' results under the circumstances" (J.A. 59). But the Commissioner's regulations explicitly provide for historical controls, and for the right to seek a waiver even of that (J.A. 488–489). Hynson never sought a waiver, and the Commissioner's decision showed the serious flaws in the submitted studies, including their controls. Since it does not deal with those studies, the Sadusk affidavit in no way controverts the Commissioner's determination.[29]

Accordingly, the Commissioner's denial of Hynson's request for a hearing and his withdrawal of approval of the NDA for Lutrexin should have been upheld by the court of appeals.[30]

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[29] If the affidavit is read to mean that, in the absence of a waiver, there is no need for controls—even historical—then it is contrary to the regulations and irrelevant for that reason.

[30] Withdrawal of the NDA does not mean that Lutrexin is forever banished from the market. Hynson is at liberty to file for approval a new NDA for Lutrexin, either with new studies or with the same studies and a request for a waiver.

CONCLUSION

For the foregoing reasons, the judgment of the court of appeals should be reversed.

Respectfully submitted.

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

72-414

[illegible]

HYNSON, WESTCOTT & DUNNING, INCORPORATED,
Cross-petitioner,

v.

ELLIOT L. RICHARDSON, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs.

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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BRIEF FOR CROSS-PETITIONER HYNSON, WESTCOTT & DUNNING, INCORPORATED

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OPINIONS BELOW

The Opinion of the Court of Appeals (J.A. 173)[1] is reported at 461 F.2d 215. The Order of the Commissioner of Food and Drugs reviewed by the Court of Appeals was

[1] J.A. refers to the single joint appendix for the five cases consolidated by the Court's order of January 8, 1973.

published in the Federal Register of June 18, 1971 (36 F.R. 11,763, J.A. 72). The opinions in two related cases decided by the Fourth Circuit, *USV Pharmaceutical Corporation* v. *Richardson* (J.A. 466) and *Bentex Pharmaceuticals* v. *Richardson* (J.A. 258) are reported at 461 F.2d 223 and 463 F.2d 363 respectively. *Ciba Corporation* v. *Richardson*, a case consolidated by the Court with the instant case and *USV* and *Bentex*, is reported at 463 F.2d 225 (J.A. 215).

JURISDICTION

The Judgment of the Court of Appeals in the instant case (No. 414) was entered May 24, 1972. On August 17, 1972, Mr. Justice Rehnquist extended the time for filing a petition for writ of certiorari to and including September 11, 1972. The petition of the Solicitor General in No. 394 and the cross-petition in the instant case were granted on January 8, 1972. Petitions in the related cases of *Bentex*, *USV* and *Ciba* were also granted on that date.

The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1) and 21 U.S.C. 355(h).

STATUTES AND REGULATIONS INVOLVED

The pertinent statutory provisions are set forth in the Joint Appendix at p. 475 *et seq.* For convenience, excerpts from such provisions are hereinafter set forth.

Federal Food, Drug and Cosmetic Act, 52 Stat. 1040, as amended by the Drug Amendments of 1962, P.L. 87-781, (Harris-Kefauver Act), 21 U.S.C. 301 *et seq*:

Section 201(p)(1) and (2), 21 U.S.C. 321(p)(1) and (2):

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal

drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

Section 505, (a), (b), (e), 21 U.S.C. 355(a), (b), (e):

(a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such person shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use. * * *

* * * *

(e) The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this

section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof. * * *

Section 107(c) of Public Law 87-781, 76 Stat. 788-789, note following 21 U.S.C. 321 (1970 ed).

(1) As used in this subsection, the term "enactment date" means the date of enactment of this Act; and the term "basic Act" means the Federal Food, Drug, and Cosmetic Act.

(2) An application filed pursuant to Section 505(b) of the basic Act which was "effective" within the meaning of that Act on the day immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application "approved" by the Secretary within the meaning of the basic Act as amended by this Act.

* * * *

(4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commer-

cially used or sold in the United States, (B) was not a new drug as defined by Section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under Section 505 of that Act, the amendments to Section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

QUESTIONS PRESENTED

The Questions involved in the instant case (No. 414) are not raised in the Government's petition in No. 394,[2] but were presented to the court below by cross-petitioner. The questions are:

(1) Whether the decision of the Court of Appeals was correct that the Commissioner of Food and Drugs was without authority to determine initially his own jurisdiction in a proceeding to withdraw a new drug application on the ground that there was a lack of substantial evidence of the subject drug's effectiveness, i.e., whether the drug is a "new drug" or, if it is a "new drug", whether it is exempt from the effectiveness requirements of the Drug Amendments of 1962.

(2) Whether one whose drug is the subject of such a withdrawal proceeding is entitled to an administrative hearing at which evidence may be introduced as a basis for deciding whether the Commissioner had jurisdiction to conduct such a proceeding.

(3) Whether a new drug application for a drug which had become generally recognized as safe on the day before

[2] The issue in No. 394 is whether Hynson, Westcott & Dunning was entitled to a hearing on the question of whether there was a lack of substantial evidence of effectiveness of Lutrexin (See Brief in Opposition to Petition for Writ of Certiorari in No. 394, p. 3.)

the effective date of the Drug Amendments of 1962 (October 9, 1962) was no longer an "effective" application within the meaning of Section 107(c)(2) of such amendments and therefore such application was not "deemed approved" under that section.

(4) Whether a drug which had become generally recognized as safe on the day before the effective date of the Drug Amendments of 1962 was a "new drug" on that date and was "covered by an effective application" within the meaning of Section 107(c)(4)(B) and (C) of such Amendments.

STATEMENT

Hynson, Westcott & Dunning, Incorporated (HW&D) has since 1953 marketed Lutrexin, a prescription drug, for use in the treatment of premature labor, second and third trimester threatened abortion, and dysmenorrhea (menstrual discomfort). The drug was, when first marketed in 1953, a "new drug" within the meaning of Section 201(p) (21 USC 321(p)), of the Federal Food, Drug and Cosmetic Act as then written (52 Stat. 1040, the "Act"). Pre-marketing clearance of Lutrexin under the new drug provisions of Section 505 of the Act, (21 USC 355) was, therefore, necessary, and a new drug application (NDA) for the drug was filed and became effective on December 23, 1953.

Until 1962 the test under Section 201(p)(1) for determining the necessity for obtaining pre-marketing clearance of a drug was whether the product was generally recognized as safe by qualified experts. Congress, in the Drug Amendments of 1962 (P.L. 87-781), amended Sections 201(p) and 505 of the Act to require pre-market clearance of new drugs for both safety and effectiveness. Thus, Section 201(p)(1), as amended, defined "new drugs" as those not generally recognized by qualified experts as both safe *and* effective for their intended uses.

Congress also, in 1962, added to Section 505(d) and (e) the concept of "substantial evidence of effectiveness," a concept separate and apart from the concept of general recognition of safety and effectiveness. The latter is solely a jurisdictional test to determine whether a drug is "new" under Section 201(p). The manufacturer of a product which was a new drug under the jurisdictional test, because of a lack of general recognition of effectiveness would, in order to obtain approval of an NDA for his product under amended Section 505, have to supply the Food and Drug Administration (FDA) with substantial evidence of the effectiveness of the drug. Likewise, where appropriate, FDA could, under Section 505(e)(3), withdraw approval of a new drug's NDA if it found a lack of substantial evidence of the drug's effectiveness.

A. Background

By notice published in the Federal Register of May 24, 1968, (J.A. 10) the Commissioner of Food and Drugs announced that FDA had reviewed and evaluated a report (J.A. 5) of the National Academy of Sciences-National Research Council (NAS-NRC) on Lutrexin;[3] that Lutrexin was found by the Academy to be "possibly effective"; that the claims made for the drug are inappropriate or unwarranted in the absence of sound documentation; and that the Food and Drug Administration had concluded the same thing. The notice offered HW&D the opportunity to submit documentation in support of the representations made for the products. HW&D submitted such data under date of November 22, 1968.

By notice published in the Federal Register of March 22, 1969, (J.A. 12) the Commissioner of Food and Drugs found that the additional data submitted by HW&D did not provide substantial evidence of the effectiveness of

[3] FDA had contracted with NAS-NRC to review the effectiveness of drugs cleared for marketing as "new drugs" between 1938 and 1962 on the basis of proof of safety only.

Lutrexin for its recommended uses. The notice offered HW&D an opportunity for a hearing "In accordance with the provisions of Section 505 of the Act (21 USC 355) and regulations promulgated thereunder (21 CFR Part 130)".

By letter to the hearing clerk of the FDA dated April 18, 1969, HW&D elected to avail itself of the opportunity for a hearing, reserving the right to contest the jurisdiction of the Commissioner and the Food and Drug Administration in the administrative proceedings, or in judicial proceedings, or in both (J.A. 14).

On August 19, 1969, HW&D filed a complaint for declaratory judgment and injunctive relief in the United States District Court for the District of Maryland (*Hynson, Westcott and Dunning, Incorporated* v. *Finch*, C.A. No. 21112), seeking a judicial determination of the status of Lutrexin under Sections 201(p) and 505 as amended in 1962 (J.A. 15).

After hearing in open court upon the Government's motion to dismiss, Judge Northrop, on September 16, 1970, dismissed the suit on the ground that the issues presented to the Court were within the primary jurisdiction of the FDA and that HW&D had failed to exhaust its administrative remedies. The order (J.A. 23) provided that HW&D's administrative remedies would enable it to "obtain an Agency determination on the record made before the Agency on the medical issues involved, on its claim that the drugs involved are generally recognized among qualified experts as safe and effective for their intended uses, its claim that they are protected from the drug efficacy review by the grandfather clause of the 1962 Amendments, and the claim that there is substantial evidence available to support the therapeutic effectiveness for which the drugs are promoted."[4]

[4] The claims of HW&D relating to "new drug" status and the grandfather provisions are sometimes referred to herein as "jurisdictional questions".

Pursuant to that order, by letter dated October 16, 1970, HW&D (J.A. 24), requested the Commissioner of Food and Drugs to reinstitute hearing procedures on the question of the proposal of FDA to withdraw the new drug application for Lutrexin, under Section 505(e) of the Act, and to grant HW&D a hearing on the jurisdictional questions, which the court had held were within the primary jurisdiction of the FDA. With that request, HW&D submitted the affidavits of expert physicians, and supporting medical data, which had been filed with the court in the Maryland litigation. By notice (order) published in the Federal Register of June 18, 1971, the Commissioner of Food and Drugs denied HW&D a hearing on any of the questions involved and withdrew "approval" of the new drug application (J.A. 72).

B. Decision Of The Court Of Appeals

The Court of Appeals held that HW&D was entitled to a hearing on the question of whether there is a lack of substantial evidence of the effectiveness of Lutrexin.[5] In addition to this point, four basic questions were before the Court of Appeals and argued in HW&D's brief: (1) whether the Commissioner of Food and Drugs was correct in his determination that Lutrexin was not exempt from both *administrative* and *judicial* enforcement of the effectiveness provisions of the Drug Amendments of 1962, by virtue of Section 107(c)(4) of those amendments; (2) whether the Commissioner was correct in his determination that Lutrexin was not exempt by virtue of Section 107(c)(2) of the 1962 Amendments, from *administrative* withdrawal of approval of its NDA under Section 505(e)(3) of the Act on the ground of lack of substantial evidence of effectiveness; (3) whether in any event the Commissioner was correct in determining that HW&D's product is a new drug subject to the provisions of Sec-

[5] That holding is before this Court for review in No. 394.

tion 505 of the Act as amended by the 1962 Amendments; and (4) whether the Commissioner was correct in denying HW&D an administrative hearing on these jurisdictional questions.

The Court of Appeals decided the first jurisdictional question adversely to HW&D, following its decision in *USV Pharmaceutical Corporation* v. *Richardson*, *supra*. It did not even mention the second and third questions. On May 23, 1972, the day before its decision in *Hynson* the Fourth Circuit had held that neither FDA nor the Court of Appeals on direct appeal under Section 505(h), 21 USC 355(h), had authority to determine the agency's jurisdiction. (*Bentex Pharmaceuticals, Inc.* v. *Richardson*, 463 F.2d 363, J.A. 258). Implicit in the Court's decision in *Hynson*, therefore, is a holding that FDA did not have the authority to consider these jurisdictional questions.

It is apparent that factual questions underlie the matter of whether Section 107(c)(2) and (4), or either of them, is applicable to Lutrexin, *viz.*, whether the drug was generally recognized as safe on the day before the effective date of the Drug Amendments of 1962 (October 9, 1962), within the meaning of Section 201(p), 21 USC 321(p), of the Act and was therefore not a new drug within the meaning of Clause (B) of Section 107(c)(4) of those amendments and not covered by an "effective" application within the meaning of Sections 107(c)(2) and 107(c)(4)(C) of the Amendments and whether the drug was being marketed in the United States on October 9, 1962, with the same labeling as is now in use, within the meaning of Section 107(c)(4). Underlying the third jurisdictional question above stated is the factual matter of whether Lutrexin is generally recognized *now* as both safe *and* effective within the meaning of Section 201(p) as amended in 1962. These are adjudicative facts determinative of the jurisdictional questions involved (See affidavits of

experts, J.A. 32 et seq.; medical literature, J.A. 87 et seq.).

Because of the *Bentex* ruling, evidence on the factual questions above-stated would not be considered by FDA or introduced at the hearing to which the Court of Appeals said HW&D was entitled since the hearing would be limited to the question of whether there is a lack of substantial evidence of the effectiveness of Lutrexin. Yet, if any one of the jurisdictional questions were decided in favor of HW&D, the question of whether HW&D is entitled to a hearing on the Commissioner's proposal to withdraw the license for its product under the new drug provisions of the Act would be moot.

SUMMARY OF ARGUMENT

1. In a proceeding to withdraw approval of a new drug application under Section 505(e)(3) of the Act, 21 U.S.C. 355(e)(3), the Food and Drug Administration (FDA) has the authority, subject to review by the Court of Appeals under Section 505(h), 21 U.S.C. 355(h), of the Act, to determine its own jurisdiction to conduct the proceedings, *e.g.*, whether a drug is a "new drug" within the meaning of Section 201(p), 21 U.S.C. 321(p).

A drug such as Lutrexin, which was once new and for which a new drug application had become effective, ceased to be "new" under the Act prior to its amendment in 1962, because it became generally recognized as *safe* by qualified experts (Section 201(p) as enacted in 1938) and is not "new" under the 1962 Amendments because it is generally recognized as both safe *and* effective.

FDA cannot properly conduct its business under the new drug section (Section 505) unless it has the authority to determine, initially, questions of jurisdiction. The decisions, including decisions of this court, clearly sup-

port our position that the agency has such authority in conducting proceedings such as the withdrawal-of-approval proceeding to which Lutrexin has been subjected.

2. The facts upon the basis of which FDA jurisdiction to conduct the withdrawal proceeding rests are adjudicative facts. Due process requires a hearing to establish the necessary facts to determine (a) whether Lutrexin is exempt from *administrative* withdrawal proceedings because of Section 107(c)(2) of the 1962 Amendments or from both *administrative* and *judicial* withdrawal proceedings by reason of Section 107(c)(4) of the Amendments, and (b) whether it is a new drug under the Act as amended in 1962.

There is a clear difference between the concept of "lack of substantial evidence of effectiveness" the basis for withdrawal of approval of an NDA under Section 505(e)(3) of the Act as amended in 1962, and the concept of general recognition of safety (Section 201(p) of the 1938 Act) and general recognition of safety *and* effectiveness (Section 201(p) as amended in 1962). The general recognition concept is solely a jurisdictional test which may be satisfied by adequate evidence of such recognition, but does not require, as the Government contends, the existence in the medical literature, of evidence of "substantial evidence of effectiveness" as used in Section 505(d) and (e) of the Act as amended in 1962. Section 201(p) contains no such requirement. The requirement appears only in Sections 505(d) and (e) and relates only to approval and withdrawal of approval, not general recognition of safety or effectiveness. The existence of studies showing substantial evidence of effectiveness therefore, although relevant, is not a *sine qua non* of a finding of effectiveness. Of course, the Act does not use the term "substantial evidence" in connection with proof of safety at all (as distinguished from proof of effectiveness). The cases do not support the position of the Government.

The facts relating to general recognition of safety as of October 9, 1962 (the day before the enactment date of the 1962 Amendments) must be ascertained in order to determine the application to Lutrexin of Section 107(c)(2) and (4) of the amendments. Whether the drug is now being marketed with the same labeling as was used on October 9, 1962, must be determined as a basis for ascertaining its status under Section 107(c)(4). Further, if Lutrexin is now generally recognized as both safe *and* effective Section 505 does not apply to it at all.

Our analysis of the medical data on Lutrexin, and the applicable cases, demonstrate, we believe, that FDA's decision of these underlying adjudicative facts without a hearing was wrong and a violation of due process.

3. Only those drugs whose NDAs were "effective" on October 9, 1962 are "deemed approved," by reason of Section 107(c)(2) of the Amendments; and only those NDAs "deemed approved" under that section are subject to withdrawal proceedings under Section 505(e) (except those *actually* approved under the Act as amended).

The NDA for Lutrexin became effective December 23, 1953. The drug had, however, become generally recognized as safe and had been used to a material extent and for a material time, prior to October 10, 1962, within the meaning of Section 201(p)(2) of the Act, as then in effect and was therefore no longer a "new drug." Since it was no longer a "new drug" on October 9, 1962, its NDA was on longer "effective" on that date and was therefore not "deemed approved."

An NDA for a drug which is no longer "new" is not "effective" in any legal sense.

As we show in the Argument, effective remedies under the Act other than administrative withdrawal of approval proceedings based on an alleged lack of substantial evidence of effectiveness, remain available to FDA.

4. It is our position that Lutrexin was not only not "deemed approved" under Section 107(c)(2) of the 1962 Amendments but is exempt from the effectiveness provisions of the Act by Section 107(c)(4) because, on October 9, 1962, it was commercially used or sold in the United States, was not then a "new drug," was not then "covered by an effective [new drug] application, and is marketed for the same conditions as it was on that date.

Section 107(c)(4) therefore protects the drug from *any* administrative or legal action based on alleged lack of effectiveness insofar as claims being made on October 9, 1962 are concerned. The legislative history reviewed in the Argument supports this position.

In the Argument we discuss the vagaries which inhere in the position of the Court of Appeals and the Government. Some of the confusion which has arisen in attempts to interpret the 1962 Amendments is clearly engendered by the imprecise language of the Amendments and their legislative history. Of the latter Senator Kefauver said: "Those in the future who attempt to study the legislative history of this measure as it passed through its various stages may be forgiven if they become somewhat confused." Clearly, however, the Government's position would deny any practical effect to the exempting provisions of Section 107(c)(2) and (4), contrary to the expressed intent of Congress.

ARGUMENT

I

THE COMMISSIONER OF FOOD AND DRUGS HAS THE AUTHORITY TO DETERMINE INITIALLY, SUBJECT TO JUDICIAL REVIEW, HIS OWN JURISDICTION UNDER THE NEW DRUG PROVISIONS OF THE ACT.

Basic Considerations and Legal Precedents

A. Introduction

The Fourth Circuit held in *Bentex* and *USV* that the Secretary (Commissioner of Food and Drugs) did not have authority in a new-drug withdrawal proceeding to ". . . adjudicate whether a drug meets the statutory criteria of a 'new drug' " and that the Court of Appeals reviewing an NDA-withdrawal order under Section 505(h) of the Act could not consider this jurisdictional question. Although the question was argued before the court in *Hynson*, the point was not mentioned by the Court in its opinion in the present case.[6] In *Ciba Corporation* v. *Richardson*, (J.A. 215) the Court of Appeals for the Third Circuit held:

> "Inherent in the grant of administrative competency to conduct and decide new drug proceedings is jurisdiction to decide whether the product in question in a given case is lawfully subject to such a proceeding. And, if the administrative agency takes jurisdiction, the same jurisdictional issue is present for judicial review on direct appeal from the administrative decision" (J.A. 216).

HW&D's position is that the jurisdictional question of whether a drug is subject to the new drug provisions of the Act may be determined in at least the following ways:

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[6] Presumably the Court relied upon its holdings in *Bentex* and *USV*.

(1) Upon a challenge to his jurisdiction in a proceeding to withdraw approval of an NDA under Section 505 (e) of the Act, the Commissioner may, based upon evidence adduced at an adjudicative hearing, determine the new drug status of the product involved, subject to judicial review.

(2) The jurisdictional question may be raised in an enforcement proceeding based on Section 505 of the Act; and

(3) A drug manufacturer may by a declaratory judgment action have the jurisdictional question resolved by a United States District Court.

B. Background

Prior to the proceedings involving the withdrawal of approval of the NDA for HW&D's product, the Commissioner had not adopted the position that the agency would entertain challenges to its jurisdiction over drugs as "new drugs" in NDA-withdrawal proceedings.

After receipt of the Commissioner's notice of an opportunity for a hearing on his proposal to withdraw approval of the NDA for Lutrexin (J.A. 12), HW&D filed with the Commissioner a letter electing to accept the opportunity for a hearing, but reserved the right to contest the jurisdiction of the Commissioner over Lutrexin as a "new drug" (J.A. 14). Thereafter, HW&D filed its complaint in the Federal District Court in Baltimore (*Hynson, Westcott & Dunning, Inc.* v. *Finch*, No. 21112) seeking a declaratory judgment that Lutrexin is not subject to regulation by the Commissioner as a "new drug."[7] At the hearing on the Government's motion to dismiss, counsel for the Commissioner agreed to the Court's suggestion that the agency consider the jurisdictional points in the administrative proceedings.

[7] See J.A. 15 for a summary of the allegations of the complaint.

The result of the District Court's Order was that for the first time the Commissioner had to make a determination on the record before it of its jurisdiction, *vel non*, over a drug product.

C. Judicial Precedents

The Fourth Circuit in *Bentex* and *USV* cited no decisions to support the proposition that the Commissioner does not have the authority to initially determine his jurisdiction over a drug as a "new drug" or to determine the coverage of the 1962 Amendments in particular cases. Neither did the third Circuit in *Ciba* present any authorities for its holding to the contrary.

There is, however, ample support in decisions by this court and lower federal courts for the *Ciba* holding that federal agencies have the inherent authority to determine initially their own jurisdiction, subject to appellate review.

As early as 1904, this court, speaking through Mr. Justice Holmes, held that a customs inspector, whose jurisdiction to deny admission of an alien was challenged, must determine his jurisdiction and if he decides it exists, go forward with administrative proceedings including review of his decision by Secretary of Commerce.[8] This court has also upheld the authority of the Bituminous Coal Commission and the Interstate Commerce Commission to decide initially, subject to appellate review, the question of the coverage of their respective statutes.[9] In the *Yonkers* case the Commission was presented with an application by a railroad company for a certificate allowing the company to abandon a portion

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[8] *United States* v. *Sing Tuck*, 194 U.S. 161 (1904).

[9] *Sunshine Anthracite Coal Co.* v. *Adkins*, 310 U.S. 381, 399-400 (1940); *City of Yonkers* v. *United States*, 320 U.S. 685, 689-692 (1944).

of an electric branch line. Under Section 1(22) of the Interstate Commerce Act, the Commission's authority to issue such certificates does not extend to electric railways ". . . which are not operated as a part or parts of a general steam railroad system of transportation." The question of the Commission's jurisdiction under Section 1(22) was not raised during the administrative hearings but was raised in petitions for reconsideration of the agency's order. These petitions were denied by the Commission without opinion, with the result that there were no agency findings concerning the Commission's jurisdiction over the electric branch line involved. This court held that the Commission should have determined the jurisdictional question upon appropriate findings based upon evidence of record. Mr. Justice Douglas put it this way:

> ". . . the determination of what is included within the exemption of § 1(22) involves a 'mixed question of fact and law.' Congress has not left that question exclusively to administrative determination; it has given the courts the final say. . . . But we deem it essential in cases involving a review of orders of the Commission for the courts to decline to make that determination without the basic jurisdictional findings first having been made by the Commission" (320 U.S. at 689).

This court has also upheld the authority of the Wage and Hour Administrator, in the first instance, to determine questions of coverage under the Fair Labor Standards Act, *Oklahoma Press Pub. Co.* v. *Walling*, 327 U.S. 186, 214 (1946), and the authority of the Secretary of Labor to determine initially the coverage of the Walsh-Healy Public Contracts Act, *Endicott Johnson Corporation* v. *Perkins*, 317 U.S. 501, 507-509 (1943). Most recently this court held that the Federal Power Commission had the authority to initially decide its jurisdiction to certificate a particular pipeline delivery when a certi-

fication proceeding to determine that question was pending before the Commission. *Federal Power Commission* v. *Louisiana Power & Light Co.*, 406 U.S. 621 (1972). Of particular importance to the case at bar is the following statement of the Court per Mr. Justice Brennan:

> "The need to protect the primary authority of an agency to determine its own jurisdiction is obviously greatest when the precise issue brought before a court is in the process of litigation through procedures originating in the [agency]. While the [agency's] decision is not the last word, it must assuredly be the first" (406 U.S. at 647).

The lower federal courts have consistently upheld the propriety of initial determination by federal agencies, of their jurisdiction, followed by judicial review. *Federal Power Commission* v. *Arizona Edison Co.*, 194 F.2d 679, 683-684 (9th Cir. 1952); *J. M. Huber Corporation* v. *Denman*, 367 F.2d 104, 111-112 (5th Cir. 1966), cert. denied, 352 U.S. 971; *Brooklyn Eastern District Terminal* v. *United States*, 302 F.Supp. 1095, 1107 (D. N.Y. 1969); *Fontaine* v. *Securities and Exchange Commission*, 259 F.Supp. 880, 884 (D. Puerto Rico 1966); *Southern Pacific Company* v. *National Mediation Board*, 223 F.Supp. 951, 952 (D. D.C. 1963).

In *Arizona Edison, supra*, the court held that the Federal Power Commission had authority to determine the coverage of the Federal Power Act, i.e., to classify a company as a "public utility" subject to regulation by the agency. The court said:

> ". . . the Company's contentions appear to be that a judicial determination of 'public utility' status must be made before the Commission can act. A review of the Federal Power Act demonstrates that its administration is unmistakably conferred upon the Commission and broad powers of rulemaking, prosecuting and adjudicating are given it. . . We think

> that the orderly procedure inherent in the statutory scheme contemplates that the Commission in the exercise of its broad regulatory powers may determine coverage of the Act. . ." (194 F.2d at 683).

In *Southern Pacific, supra,* Judge Holtzoff described the procedure that HW&D considers the proper method for resolution of jurisdictional disputes arising in NDA-withdrawal proceedings before the Food and Drug Administration. The action was one to enjoin the National Mediation Board from taking jurisdiction of a dispute. The court exercised its discretionary power to send the matter back to the agency for initial determination of the questions involved, and denied the motion for injunction, but with leave to renew if the Board failed or declined to make a ruling on the question of its own jurisdiction.[10] Judge Holtzoff stated in part:

> "The Court assumes, of course, that the National Mediation Board will hear and determine the objections to its jurisdiction before proceeding with hearing and determining the merits of the dispute and that if it finds that it has no jurisdiction it will stop at that point. If, however, it finds that it does have the jurisdiction, it would have the authority to proceed with a hearing and reach a decision" (223 F.Supp. at 952).

Based upon the foregoing precedent, it is submitted that the Commissioner of Food and Drugs could properly entertain a challenge to its jurisdiction in an NDA-withdrawal proceeding under Section 505(e), provided that appropriate procedural safeguards, including the right to an adjudicatory hearing, are employed. These matters are discussed in Point II, *infra.*

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[10] The position taken by the court is thus similar to that taken by the District Court in *Bentex,* with which we concur, *viz.,* that the District Courts and the Commissioner have concurrent jurisdiction to determine the coverage of the new drug provisions of the Act.

II

A MANUFACTURER WHOSE DRUG IS THE SUBJECT OF A PROCEEDING TO WITHDRAW APPROVAL OF A NEW DRUG APPLICATION IS ENTITLED TO AN ADMINISTRATIVE HEARING ON THE QUESTION OF WHETHER THE COMMISSIONER HAS JURISDICTION TO CONDUCT SUCH A PROCEEDING.

A. The Necessity Of Distinguishing Between Proof Of General Recognition Of Safety Or Effectiveness And Proof Of Lack Of Substantial Evidence Of Effectiveness.

(1) *Introduction*

Although some of the terms used in the new-drug provisions of the Act are not readily understood, the structure of those provisions is simple. The pertinent part of the definition of the term "new drug" in Section 201(p) is whether a drug is ". . . generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective . . ." for its intended uses.

A drug which *is* a "new drug" under Section 201(p) is subject to the requirements of the new drug provisions of Section 505. Such a new drug cannot be marketed without an approved NDA supported by "substantial evidence" of effectiveness as defined in Section 505(d) of the Act. Approval of the NDA for a new drug may also be withdrawn by the Commissioner if he finds that, for various reasons detailed in Section 505(e), there is "a lack of substantial evidence" of the effectiveness of the new drug as the quoted term is defined in Section 505(d).

The term "substantial evidence," as used in Section 505(d) and Section 505(e), means:

> ". . . evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof" (Section 505(d)).

The Commissioner has promulgated regulations specifying the principles which provide the basis for ". . . the determination whether there is 'substantial evidence' to support the claims of effectiveness for 'new drugs'" (21 C.F.R. 130.12(a)(5); J.A. 487), including the types of controls which must be utilized in studies of the effectiveness of new drugs.[11]

Under the terms of the statute it is clear that the "lack of substantial evidence" test prescribed in Section 505(d) is applicable only to proof of the actual effectiveness of drugs which fall within the definition of "new drug" prescribed in Section 201(p). A determination that a drug is not generally recognized by qualified experts as safe and effective for its intended uses, and is therefore a "new drug" under Section 201(p), is a condition precedent to the application to the drug of the new drug provisions in Section 505, including application of the "lack of substantial evidence" test in Section 505(d).

The Commissioner, however, in the order withdrawing approval of the NDA for HW&D's Lutrexin (J.A. 72) elaborated a new theory which would require a manufacturer seeking to prove its drug not to be a new drug under Section 201(p), to present proof of actual effectiveness of the drug under the "lack of substantial evi-

[11] The question of the validity of these regulations arises in No. 72-394.

dence" test prescribed in the new drug provisions of the Act. Under this theory, evidence of the type required for the marketing of new drugs under Section 505(d), including adequate and well-controlled studies, must be shown to exist as a condition precedent to the application of the test of whether a product is a new drug within the meaning of Section 201(p) of the Act.

Thus, the order withdrawing approval of the Lutrexin NDA denied HW&D a hearing on the question of whether the drug is a new drug on the following grounds:

> "No adequate and well-controlled clinical investigations published in the medical literature have been identified.[12] Therefore, there is no data base upon which experts can fairly and responsibly conclude that the safety and effectiveness of . . . . [Lutrexin] has been proven and is so well established that . . . [Lutrexin] can be generally recognized among such experts as safe and effective for . . . [its] intended uses" (J.A. 72 at 74).

We shall show below that there is no basis for this conclusion.

(2) *Legislative History*

The Government in its brief in the court below, and in its memorandum in response to HW&D's cross-petition for certiorari (pp. 6-7), argued that the legislative history of the 1962 Amendments supports its contention that "substantial evidence of effectiveness" in the form of adequate and well-controlled investigations (Section 505(d) as amended in 1962) must be identified in the medical literature in order to provide a basis for a conclusion by qualified experts that a drug is generally

[12] The "substantial evidence" test prescribed in Section 505(d) for new drugs.

recognized as safe and effective. The test for general recognition of safety and effectiveness, the government maintained, can be derived from an examination of the medical testimony presented before the Senate Subcommittee on Anti-trust and Monopoly concerning the basis for the "substantial evidence" test.[13]

The Government's reliance on this legislative history is misplaced. It is unquestionably clear that the medical testimony cited in the brief below went directly to the type of evidence needed to show the effectiveness of new drugs, under the new-drug licensing provisions of the Act (Section 505). It had nothing at all to do with the question of the evidence required to show whether a drug *is* a "new drug" or not, that is, the type of evidence required to prove general recognition of safety and effectiveness.

Although it could have done so, Congress did not require qualified experts to base their expert conclusions of general recognition on the existence of adequate and well-controlled studies in the medical literature. It could not have done so on the basis of the medical testimony cited in the Government's brief below, since that testimony had nothing to do with the type of evidence required to support an expert's conclusion that a drug is generally recognized as safe and effective. Congress was concerned with the effectiveness of "new drugs", drugs which experts did not recognize to be safe and effective. This concern led to the inclusion of "general recognition of effectiveness" in the definition of new drug, but not to a specification of the evidence upon which a qualified expert must base his conclusion as to general recognition. Congress prudently left to the qualified expert the decision of the type of evidence which would cause him to

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[13] See, *e.g.*, Hearing before the Subcommittee on Anti-trust and Monopoly, Senate Judiciary Committee, 86th Cong., 2d Sess., p. 243.

conclude that a product was generally recognized as safe and effective.

(3) *Judicial Precedents*

FDA is asking this court, in effect, to judicially amend Section 201(p)(1) by adding to the definition of "new drug" in that section the definition of the term "substantial evidence" set forth in the provisions of the Act regulating new drugs (Section 505(d)). Proof of substantial evidence of effectiveness based upon adequate and well-controlled studies would involve a showing of the actual effectiveness of a drug. No cases have been cited by the Government which accept this theory. Indeed, to adopt the theory would be to overrule a legal principle firmly established by the courts. As stated by Judge Thomsen of the Maryland federal district court in a case involving the new drug status of a product:

> "In such a case as this, the court does not decide whether the drug is safe and effective; the court lacks the necessary expertise to make that decision. * * * The question which this court must decide in this case . . . is whether the Government has shown by a preponderance of the evidence [14] that the 'drug' is not generally recognized by qualified experts as safe and effective for use. . . .' " *United States* v. *Articles of Drug Labeled "Quick-O-ver"*, 274 F. Supp. 443, 445-446 (1967).

This distinction was also made in *Amp. Incorporated* v. *Gardner*, 389 F.2d 825, 831 (2d Cir. 1968), cert. denied, sub nom *Amp. Inc.* v. *Cohen*, 393 U.S. 825, rehearing denied 395 U.S. 917: " . . . the safety of the products is not what is at issue here. The question is whether there is general recognition among qualified experts of the products' safety and effectiveness. . ."; in *United States* v. *An Article of Drug* * * * *Excedrin, P.M.*

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[14] FDA has offered no evidence in the case at bar.

CCH Food, Drug & Cosmetic Law Reporter, ¶ 40,486 at page 41,226 (D. N.Y., March 5, 1971, No. 70-C-77): "the issue is general recognition, and not whether the drug is in fact safe and effective"; in *United States* v. *Article Consisting of 36 Boxes, Etc.*, 284 F.Supp. 107 at 112 (D. Del. 1968): ". . . the question is not whether in point of fact Line Away is unsafe or ineffective. It is whether qualified experts generally recognize Line Away to be unsafe or ineffective"; and in *United States* v. *Article of Drug, Etc.*, 294 F.Supp. 1307 (D. Ga. 1968), aff'd, 415 F.2d 390 (5th Cir. 1969), where the court said:

> "The court is not required to find that the drug Furestrol is actually unsafe or ineffective for its intended uses. It must be proven . . . that Furestrol was not generally recognized by qualified experts as being both safe and effective . . . (294 F.Supp. at 1310). * * *
>
> The court does not hold that Furestrol is unsafe or ineffective; however, this court does rule that Furestrol . . . is a new drug within the meaning of 21 USC § 321(p)(1), since it is not generally recognized as safe and effective . . ." (294 F.Supp at 1311).

The requirement as a basis for the determination of general recognition of safety and effectiveness of a showing of substantial evidence of effectiveness, cannot, therefore, be justified under the Act. The decisions cited above unanimously hold that actual safety is not the proper test of the status of a drug under § 201(p)(1)—the proper test is general recognition by qualified experts.

This is not to say that the existence of adequate and well-controlled studies in the medical literature is irrelevant in determining whether a drug is generally recognized as effective. Existence of controlled studies as well as other studies in the medical literature has been held relevant to such a determination. See, *e.g.*, *United States*

v. *Article of Drug, Etc.*, 294 F.Supp. 1307 (D. Ga 1968), aff'd, 415 F.2d 390 (5th Cir. 1969). Existence of controlled studies is not, however, the sole criterion which may be utilized by qualified experts to determine the general recognition question. Congress did not specify in Section 201(p) the evidence upon which experts could decide the question. The following criteria have been considered relevant in past cases and were used by HW&D's affiants in the instant case (J.A. 32 et seq.): clinical experience in the use of the drug in treatment of patients, expertise in the disease for which the drug is indicated, knowledge of the opinions of other physician-experts concerning the safety and effectiveness of the drug, and existence in the medical literature of studies, controlled or otherwise, demonstrating the safety and effectiveness of the drug. See *United States* v. *Article of Drug, Etc.*, *supra*, at 1308-1309. In a given case the existence of well-controlled studies may indicate that the drug involved has been shown to be actually effective but the drug may nevertheless not be recognized generally by qualified experts to be effective for its intended uses. On the other hand, a drug may have enjoyed such widespread use and therapeutic success that qualified experts could conclude that it is generally recognized as safe and effective, even if no studies of any kind existed in the medical literature.

In any event the attempt to incorporate the "substantial evidence" definition into Section 201(p)(1)' is doomed to failure because of one inescapable fact: the concept of substantial evidence in Section 505(d) relates only to the effectiveness of a drug; it has no relation to the safety of a drug. Section 201(p)(1), on the other hand defines a "new drug" in terms of general recognition of *safety* and effectiveness. There is no statutory provision concerning substantial evidence of safety. The Government's position would therefore lead to the incongruous result that substantial evidence of effectiveness would be required as a condition of a determination of general

recognition of effectiveness but no such evidence would be required for a determination of general recognition of safety.

B. The Requirement Of A Hearing To Determine The New Drug Status Of Lutrexin

(1) *Introduction*

In *Hynson, Wescott & Dunning, Incorporated* v. *Finch*, (C.A. No. 21112, D. Md. 1970),[15] HW&D was prepared to offer factual proof at a trial, and is prepared to do so in a hearing before FDA, to support its contentions that Lutrexin was generally recognized as safe prior to October 10, 1962, and that the product is now generally recognized as both safe and effective. This proof was and is available in the form of expert testimony by physicians who have studied and used Lutrexin extensively, as well as in the form of literature (See J.A. 32 et seq.; 87 et. seq.). The proper and legally required method of presenting such proof should have been at an adjudicative or trial-type hearing where the expert testimony could have been tested by cross-examination, as well as by presentation of any evidence available to the government in rebuttal.

Unfortunately, however, this court does not have before it for review an order based upon any evidence adduced at a trial or hearing. The order is based upon a rejection by FDA of the evidence proffered by HW&D, in its renewed request for a hearing, dated October 16, 1970. The affidavits, studies, and other data, which will be briefly summarized below, were presented to the Agency as a showing that there exists solid evidence to support HW&D's claims of general recognition of safety prior to October 10, 1962 and of general recognition of safety and effectiveness today—evidence which clearly raises questions

[15] A summary of the Complaint in that case appears at J.A. 15.

of fact which should have been resolved in an adjudicative administrative hearing.

As a result, the order before the Court of Appeals and this court cannot be accorded the usual deference due to a determination by an expert administrative agency based upon substantial evidence[16] adduced at a hearing. *Citizens to Preserve Overton Park, Inc.* v. *Volpe*, 401 U.S. 402, 414 (1971). To defer to FDA's expertise in this case, where no hearing was held and where FDA offered no evidence to support its order, would fulfill the fears expressed by this court that "Administrative expertise would be on its way to becoming 'a monster which rules with no practical limits on its discretion'." *Baltimore & Ohio R. Co.* v. *Aberdeen & R.R. Co.*, 393 U.S. 87, 92 (1968).

(2) *Brief Summary Of Medical Data Contained In Appendix*

The safety of Lutrexin has not been questioned. The affidavits of six medical experts (J.A. 32 et seq.), as well as the medical studies (J.A. 87 et seq.), submitted to the Commissioner in HW&D's request for a hearing on the jurisdictional points demonstrate conclusively that the drug is not only safe but was generally so recognized for at least ten years before the execution of the affidavits. The affidavits and studies also demonstrate that the drug is now generally recognized as both safe and effective. All told the affiants have treated over two thousand patients with Lutrexin, in dosages of up to 36,000 units in a twenty-four hour period with no side effects to mother or child. Reports on Lutrexin have been made by seven medical experts in obstetrics and gynecology, and no side

[16] We are here, of course, using this term in the normal administrative law sense, rather than as defined in Section 505(d) of the Act.

effects were reported. A few quotations from the reports and from a statement of a member of the NAS-NRC panel which reviewed Lutrexin indicate the conclusions of the experts as to the effectiveness of Lutrexin:

(a) Dr. Majewski's first two studies report on use of Lutrexin in 79 patients threatening to give birth prematurely (J.A. 92, 99). The contractions were halted in 68.4% of the patients, giving ". . . 54 babies a longer time to gain weight and to develop within the uterus, thus increasing their chances of survival and lessening the possibility of their suffering from the congenital diseases so often associated with prematurity" (J.A. 104);

(b) Dr. Rezek's 1953 paper presents 54 cases of Lutrexin treatment of premature labor. Labor was halted in 74% of the patients for at least 28 days ". . . enabl . . . [ing] many fetuses to survive that otherwise would have died because of prematurity" (J.A. 118 at 120).

(c) Dr. Gratton's study involved 219 women with a history of premature deliveries: "After using Lutrexin in a small number of problem cases and noting the apparent beneficial effect, it was decided to utilize this drug in all cases of premature labor, threatened abortion and habitual abortion. Experience gained over approximately ten years has amply shown the value of Lutrexin in the treatment of such patients. Before using this drug, only 46% live births were obtained in 446 pregnancies, whereas with the use of Lutrexin, 79.8% live births were achieved. The differences noted with, and without, Lutrexin were highly significant (P=.001) in the entire study herein reported. Significant differences (P=.001 to .05) were observed in patients with one to five previous pregnancies" (J.A. 87 at 88-89).

(d) Dr. Willard M. Allen, one of only two physicians expert in obstetrics and gynecology on the panel of the National Academy of Sciences-National Research Council which reviewed the effectiveness of Lutrexin (J.A. 5), made in a notarized letter to HW&D the following statements concerning the drug:

> "Lutrexin contains a biologically active component (as yet unidentified structurally) which has a relaxing effect on the uterus of the laboratory animals and women. . . .
>
> "The clinical evidence which you have submitted, and which I have read carefully, does indicate that Lutrexin is beneficial in the three conditions for which it is recommended. The evidence also indicates the Lutrexin is not harmful or dangerous either to the patient or to the fetus. . . . (J.A. 47-48).

(3) *Judicial Precedents*

This court has stressed the importance of the requirement that administrative decisions be based on ". . . substantial evidence and reasoned findings—which alone make effective judicial review possible. . . ." *Baltimore & Ohio R. Co.* v. *Aberdeen & R.R. Co.*, 393 U.S. 87, 92 (1968). The jurisdictional question of whether a product is generally recognized as safe and effective for its intended uses and is, therefore, a new drug, involves a mixed question of fact and law. *City of Yonkers* v. *United States*, 320 U.S. 685, 689. The affidavits of medical experts and medical studies submitted by HW&D in support of its request for a hearing on the general recognition question were certainly adequate to raise genuine and substantial issues of fact requiring resolution at an adjudicatory hearing. The Commissioner offered no affidavits or medical data in support of his denial of a hearing.

Under these circumstances the Commissioner's order violated due process of law. *Goldberg* v. *Kelly*, 397 U.S. 254, 269-270; *ICC* v. *Louisville & N.R. Co.*, 227 U.S. 88, 93-94 (1913). As stated by Mr. Justice Brennan in *Kelly*, *supra*, "In almost every setting where important decisions turn on questions of fact, due process requires an opportunity to confront and cross-examine witnesses" (397 U.S. at 269).

In any event, even had the Comissioner presented affidavits in support of his conclusion that Lutrexin was not a new drug, an adjudicative hearing would have been required. The situation would be analogous to that which arises on cross-motion for summary judgment supported by affidavits in District Court cases on the question of whether a drug is generally recognized as safe and effective. Although some doubt existed on the point in earlier decisions,[17] the law seems settled that when genuine differences of opinion exist among experts as to whether a drug is generally recognized as safe and effective, these differences present factual issues requiring a trial. *United States* v. *Article Consisting of 36 Boxes, Etc.*, 284 F.Supp. 107, 113 (D. Del. 1968), aff'd. 415 F.2d 369 (3rd Cir. 1969); *United States* v. *7 Cartons, More or Less, Etc.*, 293 F.Supp. 660, 662-663 (D. Ill. 1968);[18] *Lemmon Pharmacal Co.* v. *Richardson*, 319 F.Supp. 375, 378 (D. Pa. 1970); Cf. *United States* v. *Article of Drug* *** *"Mykocert,"* 345 F.Supp. 571, 574-575 (D. Ill. 1972).

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[17] See, *e.g.*, *Merritt Corporation* v. *Folsom*, 165 F.Supp. 418 (D. D.C. 1958); cf. *AMP, Inc.* v. *Gardner*, 389 F.2d 825, 831 (2d Cir. 1968), cert. denied, 393 U.S. 825, and *United States* v. *1,048,000 Capsules, More or Less, etc.*, 347 F.Supp. 768, 770-771 (D. Tex. 1972).

[18] The case was appealed, 424 F.2d 1364 (7th Cir. 1970). The decision of the District Court on the new drug question was not adopted by the Seventh Circuit since the case could be disposed of on other grounds.

The Commissioner in his order withdrawing approval of the Lutrexin NDA, denied HW&D a hearing on the ground that the data submitted by HW&D did not show existence of adequate and well-controlled studies in the medical literature.[19] The Commissioner attempted to support the denial with a factual analysis of the studies submitted by HW&D in its request for a hearing (J.A. 72, 74). Even if it be assumed that "adequate and well-controlled studies" are necessary for a determination that a drug is generally recognized as effective, the Commissioner's analysis itself demonstrates the existence of substantial issues of fact which cannot appropriately be resolved by a reviewing court without the benefit of a record based upon expert evidence adduced at a hearing before FDA.

The Commissioner said, for example:

(1) With respect to Dr. Majewski's first two studies: ". . . Six patients received the drug for less than three hours, which the authors without explanation considered too short a time for a true test of effectiveness" (J.A. 72, 75).

(2) With respect to Dr. Majewski's third study: "Substantiating documentation to establish an historical control and percentage of patients with medical or surgical complications of pregnancy is not provided. . . . The data in Table I does not admit of statistical evaluation by the chi square test since the test is based on the assumption that each number in the columns of Table I is the sum of independent yes or no responses. . . ." (J.A. 72, 75).

(3) With respect to Dr. Rezek's first study: "Concomitant medication is not excluded * * * No explanations of the methods of observation, the

[19] The lack of legal basis for this approach is discussed in Point II A.

recording of results, and steps taken to minimize patient and investigator bias are provided" (J.A. 76).

(4) With respect to Dr. Gratton's study: The pairings of live births percentages in Table II cannot be compared since the number of previous pregnancies differs between the pair percentages and there is no data on possible factors of previous abortions and premature labor." (J.A. 76).

These purport to be findings of fact which obviously are considered material by FDA. The findings raise issues of fact as to the nature of the studies which can be resolved only by expert testimony at a hearing. As stated by the Court below in connection with denial of a hearing by FDA on the proposal to withdraw the Lutrexin NDA:

> "Assuming that all the objections by the Commissioner . . . [to the HW&D studies] may have some validity, they do not justify a final conclusion . . . that it 'clearly appears' that there is no genuine issue of fact . . .; at most they merely create a genuine question of fact to be resolved at a hearing upon proper evidence" (J.A. 173, 180).

Without the benefit of a full record based upon expert testimony as to the medical and scientific validity of FDA's objections and the affidavits and studies themselves, a reviewing court is not in a position to decide the complex questions involved. Criticisms such as "the data . . . does not admit of statistical evaluation by the chi-square test . . ." raise questions of fact which can be resolved only by experts.[20]

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[20] See *United States* v. *1,048,000 Capsules, More or Less, Etc.*, 347 F.Supp. 768, 773-776 (D. Tex. 1972) for examples of the type of expert testimony needed to enable a court to determine both the questions of general recognition and of adequate and well-controlled studies. The court stated in that case, in connection with its

We have shown, *supra*, that the affidavits and medical literature submitted to FDA pose factual questions whose resolution is a prerequisite to a determination of whether FDA has jurisdiction under Sections 201(p) and 505 of the Act, *e.g.*, whether Lutrexin was generally recognized as safe on the day before the enactment date of the 1962 amendments (i.e. on October 9, 1962) and was therefore not a "new drug" under Section 201(p) as then in effect and whether Lutrexin is now generally recognized as both safe *and* effective and is therefore not a "new drug" under Section 201(p) as amended by the 1962 Amendments.

The situation is clearly distinguishable, therefore, from that in *Dyestuffs & Chemicals, Inc.* v. *Flemming*, 271 F.2d 281 (8th Cir. 1959), where petitioner was held not entitled to a hearing before the Secretary (FDA) upon a matter with respect to which the Supreme Court had held (*Flemming* v. *Florida Citrus Exchange*, 358 U.S. 153 (1958)) that he had no authority to act. In *Dyestuffs* the Court said—

> "Where the objections stated and the issues raised thereby are, even if true, legally insufficient, their effect is a nullity. . . ." 271 F.2d at 286.

Obviously that is not the situation here since the facts cross-petitioner has already presented indicate that FDA does not have the jurisdiction which it claims over Lutrexin.

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discussion of testimony on the question of a product's "new drug" status:

> "It is a substantive area in which the layman including this court can readily lose his way in a morass of technical terms, which, once comprehended, serve to bridge and lead to an understanding of the professed uses of Afrodex in the pharmacological, medical and psychiatric fields. Whatever the extent of this litigation, this articulation of expert opinion should assist in graphically underscoring the reasons why this court is persuaded to hold as it does today" (347 F.Supp. at 773).

Nor is this case like *Sun Oil Co.* v. *Federal Power Commission*, 256 F.2d 233 (5th Cir. 1958), cert. denied, 358 U.S. 872 where no fact question was involved and the court found that "The only benefit that would have inured to Sun by notice and hearing would have been the privilege of making a legal argument before the Commission", which neither due process nor the statute required (256 F.2d at 240-241); or *United States* v. *Storer Broadcasting Company*, 351 U.S. 192 (1956), where petitioner concededly "owned" more television stations than a rule of the Federal Communications Commission permitted; or *Federal Power Commission* v. *Texaco, Inc.*, 377 U.S. 33 (1964), where a petition was patently not in proper form because of certain price-changing provisions in the contracts filed with the petition, which were not permissible under a rule of the Commission.

The "Rules of Evidence for United States Courts and Magistrates" (Federal Rules of Evidence) were adopted by the Supreme Court November 20, 1972, to take effect July 1, 1973. (468 F.2d—No. 2, Advance Sheets, January 1, 1973, p. 1). In its notes on Rule 201, entitled "Judicial Notice of Adjudicative Facts," the Advisory Committee stated that its note "draws extensively" upon the writings of Professor Davis (Id. at 18) and quotes from his definition of adjudicative facts in his Administrative Law Treatise, Section 15.03, p. 353, as "those to which the law is applied in the process of adjudication. . . . They relate to the parties, their activities, their properties, their business" Id. at 20. Adjudicative facts are distinguished from legislative facts which are those upon the basis of which the applicable law and policy have been previously established. Administrative Law Treatise at p. 353.

We think it clear that the facts involved in a determination of whether Lutrexin is within the coverage of the Act and the 1962 Amendments are adjudicative

facts. They relate to the activities and business of Hynson, Westcott & Dunning in its marketing of Lutrexin under rules previously established by Congress. Thus, the questions of general recognition of safety or effectiveness of the drug, and of what labeling it bore on the day preceding the enactment date of the 1962 Amendments can relate only to Lutrexin. The answers to those questions are not pertinent to any other drugs or their status under the Act.

The law requires a trial-type hearing to determine those facts. Davis, Administrative Law Treatise, 1970 Supplement, Sections 7.01, 7.04.[21] Such a hearing may be held as a part of or ancillary to the trial-type hearing which the Fourth Circuit held was required in a proceeding to determine whether there is a lack of substantial evidence of the effectiveness of Lutrexin, which also involves adjudicative facts. (The necessity for a hearing on the question of whether there is a lack of substantial evidence of the effectiveness of Lutrexin will be discussed in our reply brief in *Richardson* v. *Hynson, Westcott & Dunning*, No. 394).

It is apparent from the leading case of *Myers* v. *Bethlehem Shipbuilding Corporation*, 303 U.S. 41 (1938) that an agency, in determining the question of its own jurisdiction, must do so on the basis of evidence adduced at a hearing. There is nothing in the Federal Food, Drug and Cosmetic Act to justify a different conclusion on this point than that reached in *Myers*.

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[21] It is our view that such a hearing should have been afforded by the District Court in *Hynson, Westcott & Dunning* v. *Finch* (CA No. 21112, D. Md., September 11, 1970, J.A. 23), but that it must be afforded administratively in a withdrawal proceeding under Section 505(e)(3) if it has not been decided in the Courts and is made an issue by a party.

If the adjudicative facts on the question of coverage are found to be contrary to the present position of the agency, either by the Agency or the Court of Appeals, the withdrawal proceeding will become irrelevant and moot.

III

LUTREXIN WAS NOT "DEEMED APPROVED" UNDER SECTION 107(c)(2) OF THE DRUG AMENDMENTS OF 1962 AND HENCE WAS NOT SUBJECT TO ADMINISTRATIVE WITHDRAWAL PROCEEDINGS UNDER SECTION 505(e)(3) OF THE ACT.

Section 107(c)(2) of the Drug Amendments of 1962 provides that—

> "(c)(2) An application filed pursuant to Section 505(b) of the basic Act which was 'effective' within the meaning of that Act on the day immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application 'approved' by the Secretary within the meaning of the basic Act as amended by this Act."

In 1962 Section 505 of the Act was amended to read in terms of "approval" of an application, replacing the language of the Act as enacted in 1938, which referred only to applications becoming "effective." Thus, Section 505(e) authorizes the Secretary (Commissioner) to "withdraw approval" of an application "(3) . . . if there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have . . .".

Consequently, only applications "deemed approved" under Section 107(c)(2), or actually approved under the Act as amended in 1962, can be subject to withdrawal of approval proceedings.

The day immediately preceding the enactment date of the 1962 Amendments was October 9, 1962. An appli-

cation which was "effective" on that date is "deemed approved" under Section 107(c)(2) and therefore was subject to administrative withdrawal proceedings under Section 505(e)(3) of the Act on the ground of lack of substantial evidence of effectiveness. But such withdrawal proceedings, based on old claims effectiveness, could not be brought for two years after the enactment dates of the 1962 amendments because of Section 107(c)(3)(B).

FDA contended below that Lutrexin was "deemed approved" and "approval" was, therefore, subject to withdrawal under Section 505(e)(3) two years after the enactment date. This theory was cited as legal support for its withdrawal order (J.A. 72, 74).

Concededly, however, the NDA for Lutrexin was never *actually* approved by FDA since, in 1953, when it was filed and reviewed by FDA, there was no provision for approval of NDA's. They simply became "effective" after a stated statutory period unless they were denied.

It is our position, which is supported by the affidavits of experts reproduced in the Joint Appendix (p. 32 et seq.), that Lutrexin had, as of the day before the enactment date of the 1962 Amendments, become generally recognized as safe and had been used to a material extent and for a material time, within the meaning of Section 201(p)(2) of the Act as then in effect, and was therefore no longer a new drug. Since it was no longer a new drug on October 9, 1962, the NDA for Lutrexin was no longer "effective" on that date and was therefore not "deemed approved" under Section 107(c)(2) of the 1962 Amendments.

A "new drug" could not be marketed under the 1938 Act without an "effective" NDA. It is clear that an "effective" application is one which authorized the marketing of the "new drug" which is the subject of the

application. If the drug is no longer "new" within the meaning of the Act (Section 201(p), 21 USC 321(p)), it is apparent that the application has no legal effect at all. Thus, if FDA purported to approve an application for a drug which was not a "new drug" within the meaning of Section 201(p), the application could not become legally "effective". It is the same where a drug was no longer "new" on October 9, 1962, and therefore no application was "effective" with respect to it on that date.

Otherwise stated, an NDA of a drug which is no longer new has no viability—is of no legal effect. Neither in logic nor law can there be an "effective" *new drug* application for a drug which is not a *new drug*. Certainly this approach reflects the ordinary meaning of the term "effective" and, in the absence of an indication in the statute or its legislative history the ordinary meaning should, we submit, be accepted.

It should be emphasized that our conclusion that Lutrexin was not "deemed approved" excuses it from administrative withdrawal of approval of its NDA under Section 505(e)(3), but not from judicial proceedings under Section 505, such as seizure, criminal prosecution and actions for injunctions based on allegations of a lack of general recognition of effectiveness.[22] It is exempt from these judicial proceedings only if it meets the three conditions of Section 107(c)(4) hereinafter considered (Point III) and then only with respect to old claims of effectiveness being made on October 9, 1962.

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[22] Section 505(a), 21 U.S.C. 355(a): "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug." Section 301, 21 U.S.C. 321: "The following Acts and the causing thereof are hereby prohibited: . . . (d) The introduction or delivery for introduction into inter-state commerce of any article in violation of section . . . 505."

If scientific developments should result in a re-evaluation by qualified experts and a reversal of their recognition of safety. FDA could proceed in the District Court against the drug on the ground that it had again become a new drug under Section 201(p). Moreover, if the agency believes that the claims of effectiveness for an exempt drug are false or misleading it can proceed against them under Section 502(a) of the Act. There is no exemption from such proceeding.

FDA is therefore not without effective remedies. The fact that it cannot challenge the status of drugs such as Lutrexin under Section 505(e)(3) with respect to old claims of effectiveness results from a deliberate choice of the Congress.

IV

LUTREXIN IS EXEMPT FROM THE EFFECTIVENESS REQUIREMENTS OF THE 1962 AMENDMENTS BY REASON OF SECTION 107(c)(4) OF THOSE AMENDMENTS.

Section 107(c)(4) of the 1962 Amendments (J.A. 482) makes the effectiveness requirements of the amendments inapplicable to drugs which on or before October 9, 1962, (A) were being commercially used or sold in the United States, (B) were not "new drugs" and (C) were not then "covered by an effective [new drug] application, *"if the labeled conditions of use are the same as on that date."*

This provision protects a drug which meets the three conditions, not only from administrative withdrawal of approval of its NDA under Section 505(e)(3) of the Act but also from seizure, criminal or injunctive proceedings, instituted on the ground that the drug fails to comply with the effectiveness requirements of the 1962 Amendments. New claims, however, are not protected.

There is no doubt that Lutrexin meets the criterion of Clause A of Section 107(c)(4), i.e., that the drug was commercially used or sold in the United States on October 9, 1962. We believe that the literature and annexed affidavits (J.A. 87 et seq.; 32 et seq.) support our view that it was not a "new drug" (Clause B) on that date because it was generally recognized as safe and had been used to a material extent and for a material time within the meaning of Section 201(p)(2) as then written. If the court does not accept our view based on the record, we submit that no determination can be made on the matter without a hearing before FDA at which witnesses, including members of the NAS-NRC panel which evaluated the drug, may appear for examination and the evidence can be analyzed.

In our view also, Lutrexin was not "covered by an effective application" on October 9, 1962, within the meaning of Clause (C) of Section 107(c)(4) since, contrary to the FDA theory, there was no "effective" application at that time and consequently the drug could not have been "covered."

The Court of Appeals held that Lutrexin was not exempt under Section 107(c)(4) of the 1962 Amendments because approval of its NDA had not been withdrawn by FDA under Section 505(e). This construction distorts the purpose and effect of Section 505(e) and makes Section 107(c)(4) virtually meaningless.

The *purpose* of Section 505 (e) is to prevent the further shipment of a new drug in interstate commerce based upon a finding that it is unsafe or ineffective or otherwise fails to conform to the standards set up in Section 505 (e). Obviously, this purpose is entirely inconsistent with the effect which the court attributes to such withdrawal, *viz.*, that it operates as a condition of the exemption of the drug under Section 107(c)(4).

Thus, the bizarre result of the court's ruling would be that such a drug (including Lutrexin) could become exempt by reason of withdrawal of approval under Section 505(e), whereas the intended effect under the statute is to prevent the shipment of the drug in interstate commerce on the basis of the FDA view that it is still a new drug which does not comply with Section 505.

A construction so clearly inconsistent with the purpose of the statute should not be allowed to stand.

Our position that a drug which was no longer "new" (within the meaning of Section 201(p)(2) and Clause (B) of Section 107(c)(4) of the 1962 Amendments), was not "covered by an effective application" under Clause (C) of Section 107(c)(4), was rejected by the Court of Appeals in *USV*[23] on the ground that it would make surplusage of Clause (C).

By the same token, if, as FDA maintains, and the Court of Appeals agreed, every drug which had gone through the new drug procedures and had thereafter ceased to be a new drug was nevertheless "covered by an effective application" within the meaning of Clause (C), then Clause (B) would be surplusage; for if such a drug is "covered by an effective application" despite having lost its new drug status, the test of whether it is no longer a new drug (Clause (B)) would be useless.

A drug which was a "new drug" on October 9, 1962 (Clause (B)) could not be "covered by an effective application" (Clause (C)) if no NDA had been filed for it or if an NDA had been filed but had not been permitted to become effective under the Act before its admendment in 1962. These, then, are other situations in which either Clause (B) or (C) would be surplusage.

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[23] *USV Pharmaceutical Corporation* v. *Richardson*, 461 F.2d 223, J.A. 469-470.

It is the Government's position, as we have noted, that every drug which has gone through the new drug procedures and thereafter ceased to be a new drug is nevertheless "covered by an effective application" within the meaning of Clause (C) of Section 107(c)(2) of the 1962 Amendments and that this principle even extends to "me-too" [24] drugs despite the fact that the "me-toos" were never the subject of NDAs.

The Fourth Circuit stated in *USV* with respect to Section 107(c)(4): "The Congress never intended that a drug being marketed under an approved NDA might qualify under the 'grandfather clause.' This is plain from the comment of the Conference Committee Report that the exemption was to apply 'to existing labeling claims of drugs that have never previously been subject to the new-drug procedure.'" J.A. 470, 461 F.2d 223 at 227. It is our position that, since Lutrexin was no longer a new drug on October 9, 1962, it was not then being marketed under an NDA.

This approach of the Government and the Court of Appeals seems to render meaningless the term "effective application" as used both in Sections 107(c)(2) and 107(c)(4)(C) and would defeat the intention of Congress to exempt some drugs from the effectiveness provisions of the 1962 Amendments.

Thus, if every drug which has gone through the new drug procedures and all "me-too" drugs are "deemed approved" because their NDAs were allegedly "effective" on October 9, 1962, apparently no drug could meet the condition of Clause (C) of Section 107(c)(4) of the amendments that it be "not covered by an effective application," except a new drug (other than a "me-too" drug) for which no NDA has ever been filed.

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[24] Drugs which were copies of drugs which were the subject of NDAs but then became "old drugs," thereby making unnecessary the filing of NDAs for the copies.

The Government leans upon the statement of President Kennedy that a principal purpose of the amendments which he proposed to S. 1552, then pending (August 6, 1962) was: "to assure the American people that any drug on the market today is safe and effective for its intended use." The President's proposal, as presented by Senator Kefauver, and as it appeared in the original Harris bill (HR 11581), provided for the revocation of the effectiveness of an NDA if the Secretary finds—

> "(1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe or ineffective, *or show that there is substantial doubt as to the safety or effectiveness of such drug . . .*"[25] (Emphasis supplied)

This is *not* the provision adopted by the Committee. The provision adopted by the Committee and passed by the Congress is Section 505(e) which provides for withdrawal of "approval" if the Secretary finds, after due notice and opportunity for a hearing, that—

> "(3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have . . .

Even a cursory comparison of the two revocation provisions reveals that this one is vastly more restrictive upon the Secretary than that recommended by the President and Senator Kefauver. As Senator Hruska said of suspension of an application on the basis of "substantial doubt" as proposed by the President and Senator Kefauver—

> "However, 'substantial doubt' is a slippery, elastic term, permitting suspension whenever the Secretary

[25] 108 Cong. Rec. 16230, August 22, 1962.

> feels like it, without hope of meaningful judicial review" [26]

Apparently the Government interprets §§ 107(c) and 505(e)(3) as if the provision proposed by Senator Kefauver had been enacted into law, whereas, to the contrary, the Kefauver proposal was rejected by the Committees of both the Senate and the House and by those bodies themselves. Even if the proposals had been accepted it is difficult to see how that fact would support the proposition of the Government which would subject every drug which had ever gone through the new drug procedure to re-evaluation as to efficacy.

Complementing the basic considerations above discussed is the circumstance that the language of §§ 107(c)(3)(A) and (4) of the Amendments leads clearly to the conclusion that only *new claims* of effectiveness for old drugs whose NDAs became effective prior to October 10, 1962, were subject to the amendments. This view is supported by the legislative record of S. 1552, which, as revised, became the 1962 Amendments.

When the bill, as originally reported by the Senate Judiciary Committee, was changed to expand the definition of "new drug" to include drugs not generally recognized as effective, the Committee stated—

> "A question arose as to the circumstances and extent to which a *new claim or change of claim* of effectiveness made after the initial approval of a new drug application could be made without supporting evidence to be submitted to the Department under the new-drug procedure. In order to eliminate any possible ambiguity on this point the term 'effectiveness' is employed in the committee's substitute amendment" (Emphasis supplied, S. Rep. No. 1744, Part II, 87th Cong., 2d Sess. 5).

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[26] 108 Cong. Rec. 10108, June 11, 1962.

Likewise, on the floor, Senator Eastland, consistently with the language of Sections 107(c)(2),(3) and (4), said that, with the addition of "effectiveness" to the definition "every brand new product, and every new claim for an existing product, would be subject to the tests and procedures established in § 505 of the Act" (108 Cong. Rec. 16304, August 23, 1962).

There is nothing inconsistent with these explanations in the history of HR 11581, the companion bill to S. 1552.

It must be clear from the legislative history as well as from the terminology of the 1962 Amendments themselves that statements in the Committee Reports and in debate relating to withdrawal of approval of NDAs on the grounds of lack of effectiveness after two years from October 9, 1962, referred only to withdrawal of approval of NDAs for drugs which were still *new drugs* on that date.

It is our view that a provision of this nature, concededly not artfully drafted, should not be construed to deny effect to Congress' undoubted intention to exempt some drugs from certain obligations under the 1962 amendments. Yet that is the effect of the decision of the Fourth Circuit. FDA would go even further and deprive the provision of any practical effect at all.

We do not claim that the language and legislative history of the Drug Amendments of 1962 is crystal clear in all respects. In fact, Senator Kefauver, an active sponsor of the bill which became the 1962 Amendments stated—

> "Those in the future who attempt to study the legislative history of this measure as it passed through its various stages may be forgiven if they become somewhat confused. In my experience there have

been few bills which have had so varied a legislative history." [37]

We do maintain, however, that the language of the amendments and their history evince a purpose by Congress to exempt some drugs, such as Lutrexin entirely from the effectiveness provisions of the amendments except for new claims.

This does not mean that judicial remedies are not available to FDA to deal with such drugs in matters other than the effectiveness requirements of the 1962 Amendments. All such remedies may properly be invoked and no new claims of effectiveness (any not in use on October 9, 1962) are exempt under Section 107(c)(4).

V

CONCLUSION

The New Drug Application for Lutrexin was not "deemed approved" under the provisions of Section 107(c)(2) of the Drug Amendments of 1962 and is therefore not subject to *administrative* withdrawal proceedings under Section 505(e)(3) of the Act as amended, based on allegations of a lack of substantial evidence of effectiveness to support old claims for the drug, i.e., claims which were being made as of October 9, 1962.

Moreover, Lutrexin is entitled to the broader exemption provided by Section 107(c)(4), from *any* legal proceedings based on the effectiveness requirements of the 1962 Amendments. The exemption does not extend to other legal proceedings under the Act.

HW&D is entitled to an administrative hearing before FDA on the question of whether FDA has jurisdiction despite the provisions of Sections 107(c)(2) and

[37] 108 Cong. Rec. 22037, October 3, 1962.

107(c)(4) to withdraw the old NDA for Lutrexin on the ground that there is a lack of substantial evidence to support the old claims for its effectiveness. It is also entitled to such a hearing on the question of whether Lutrexin is now generally recognized as both safe *and* effective and therefore not subject to FDA's jurisdiction under any provision of Section 505.

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